TO STUDY THE CORRELATION OF LIVER STIFFNESS MEASUREMENT AND HEPATOCELLULAR CARCINOMA

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Submitted By

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I hereby declare that the thesis entitled "**TO STUDY THE CORRELATION OF LIVER STIFFNESS MEASUREMENT AND HEPATOCELLULAR CARCINOMA"** submitted towards partial fulfillment of the requirements for the award of **MD in General Medicine** degree to BFUHS is a compilation of original work carried out by me under the supervision of **Dr. Dinesh Gupta**, Professor & Head, Department of Medicine, **Dr. Kavita Saggar**, Professor & Head, Department of Radiology and **Dr. Varun Mehta,** Professor, Department of Gastroenterology. No part of this thesis has formed the basis for the award of any degree previously.

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Dedicated

to

my Family

&

Teachers

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Dr. Abhinav Garg

LIST OF ABBREVATION

AFP	Alpha fetoprotein
ARID1A	AT-Rich interactive domain containing protein
APHE	Arterial phase hyper enhancement
AUROC	Area under receiver operating characteristics
CI	Confidence interval
CT	Computerized tomography
CAP	Controlled Attenuation parameter
CTNNB1	Beta Catenin
DAA	Direct acting antiviral
FIB-4	Fibrosis score
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HCC	Hepatocellular carcinoma
HR	Hazard ratio
IQR	Inter quartile range
KPA	Kilopascals
MRI	Magnetic resonance imaging
LIRADS	Liver imaging reporting and data system
LSM	Liver stiffness measurement
NAFLD	Nonalcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
PAGE-B	Platelet, age, gender, hepatitis B score
SVR	Sustained virological response
TERT	Telomerase reverse transcriptase
TE	Transient elastography
USG	Ultra-Sonography
WNT	Wingless related integration site

ABSTRACT

Background: Liver biopsy has been traditionally used a standard method of evaluating liver fibrosis. However, because of its invasiveness, diversity of sampling and diagnostic variability this method is not widely used clinically. Recently, a new method using shear wave elastography has almost replaced liver biopsy as a tool to predict long term prognosis or the occurrence of Hepatocellular Carcinoma (HCC).

Aim: To study the correlation of liver stiffness measurement and development of Hepatocellular Carcinoma.

Methods: We compared LSM in 60 patients, out of which 30 patient had cirrhosis without hepatocellular carcinoma and 30 patients had cirrhosis with hepatocellular Carcinoma in the Department of Medicine and Department of Gastroenterology at Dayanand Medical College and Hospital, Ludhiana from October 2019 to March 2021.

Results: Patients with HCC had higher LSM than patients without HCC [55.45 +/- 16.93 v/s 30.99 +/- 19.96], P<0.0001. Multivariate analysis suggested liver stiffness (p value 0.011) and age (p value 0.010) as an independent factor for HCC, age and etiology. SSLR for HCC presence by liver stiffness was 0.2 (95% confidence interval 0.08-0.52) in <30 kPa, 1 (95% confidence interval 0.32-3.10) in <30-50kPa and 4.2 (95% confidence interval 1.82-9.67) in >50 kPa.

Conclusion: In patients with cirrhosis without HCC, a wide range of LSM is observed according to the cause of the underlying liver disease and the presence of HCC is associated with higher values in these patients. A cut-off 39.45 kPa is useful with a sensitivity of 83% and a specificity of 80% for predicting the presence of HCC.

Keywords: FibroScan, Liver stiffness measurement, Hepatocellular carcinoma

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INTRODUCTION

Hepatocellular Carcinoma (HCC) is the 6th most common cancer in terms of incident cases and accounts for ~7% of all cancers worldwide[1,2]. Liver cancers are the fourth most common cause of cancer related deaths worldwide[1]. The development of HCC depends upon various risk factors, including etiology of liver disease, race, ethnicity, sex, age, and so on. However, the presence of advanced liver fibrosis is the most important and common risk factor in Chronic Liver Disease patients[1,2]. Cirrhosis is a premalignant condition and about 80-90% of Hepatocellular Carcinoma develop on the background of cirrhosis[3].

Chronic liver disease(CLD) is usually related to hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, alcohol intake and hepatic steatosis including non-alcoholic fatty liver disease(NAFLD) and non alcoholic steato hepatitis, autoimmune liver disease, inborn errors of metabolism[1,2].

Historically Liver biopsy has been the standard method for assessing liver fibrosis and steatosis in the last few decades. However the sensitivity of liver biopsy is below 80% and its use is limited by sampling errors, inter- and intra-observer variability and possibly morbidity and mortality[4,5,6]. The average size of liver biopsy is 15 mm in length, which is 1/50000 the size of the entire liver. Pain and hypotension are the predominant complications for which hospitalization is required[7]. Clinically significant intra peritoneal hemorrhage is the rarest but most serious bleeding complications of percutaneous liver biopsy. Inadvertent puncture of Gall bladder may lead to choleperitoneum. Also cost of performing Liver biopsy is high as it includes procedure cost, in-hospital admission cost, charges of specialist doctor, nursing care and histological examinations.

Liver biopsy is associated with many complications which can be sometime life threatening and this has stimulated research into non invasive methods of fibrosis assessment, that should be liver specific,

easy to perform, reproducible, accurate and inexpensive. In addition, that non-invasive marker should be able to stage liver fibrosis as well as monitor disease progression and treatment efficacy. Currently the non-invasive markers of liver fibrosis includes serum biomarkers, axial imaging and transient elastography.

Usually Hepatocellular Carcinoma is diagnosed by Ultrasonography, Biochemical markers, Computed tomography, Magnetic resonance imaging and contrast enhanced ultrasonography[8,9]. These are excellent in diagnosing Hepatocellular Carcinoma however radiation, cost and inter-observer bias are an important drawback.

A recently introduced technique, transient elastography, non invasively measures hepatic elasticity, or stiffness[7,8]. Recent studies have reported that severe liver disease is associated with high LSM values[9,10], and also complications such as portal hypertension have more occurrence in patients with high LSM values.[10,11]An ultrasound transducer probe is mounted on the axis of a vibrator. Vibrations of mild amplitude and low frequency (50Hz) are transmitted by the transducer and an elastic shear wave is generated and its propagation velocity in the liver is measured with pulse-echo ultrasound[7]. The stiffer the tissue, faster the shear wave propagates. The propagation velocity of shear waves is directly proportional to the square root of stiffness of liver. Liver fibrosis is considered to be the largest contributor to the liver stiffness thus measured. Transient Elastography measures liver stiffness in a volume that approximates a cylinder 1 cm in diameter and 4 cm in length, between 25 to 65 mm underneath the skin surface, this volume is at least 100 times bigger than a biopsy sample, and therefore should be more representative of liver parenchyma[7]. Results of liver stiffness measurement (LSM) are expressed in kPa and it corresponds to the median of 10 validated measurements. Results are considered reliable if ≥10 measurements are acquired which are valid, also the success rate which is defined as number of valid acquisitions divided by the number of attempts is over

60%, and ratio of inter quartile range to the median of 10 measurements(IQR/M) is ≤ 0.3.[7]

Patients with compensated cirrhosis that are patients of CTP class A are not usually screened to detect portal hypertension or occurrence of small hepatocellular carcinoma. In routine practice, selection of CTP class A patients at higher risk of such complications is still difficult using bio clinical parameters, alone or combined. One can hypothesize that variations of LSM value may have a clinical relevance and help to refine the prediction of cirrhosis outcome.

There are many factors which influence the risk of HCC occurrence in patients with cirrhosis, among them liver fibrosis has been widely assessed in clinical and basic studies,[12-16]and large prospective studies have clearly established that the severity of liver disease reflected by hepatic failure or portal hypertension is associated with an increased risk of HCC.[17-19]

Our hypothesis is that the LSM, by reflecting both the amount of liver fibrosis and the severity of cirrhosis, might be used in the future as a tool to select patients with cirrhosis at higher risk of HCC occurrence. Few studies have validated the relationship between liver stiffness and the presence of HCC. This study is an attempt to add to the pool of research for finding a new non invasive method of investigation for assessing risk assessment of Hepatocellular carcinoma, as TE has the advantage of being painless, rapid(usually less than 5 min) and easy to perform at the bedside or in the outpatient clinic.

AIMS AND OBJECTIVES OF THE STUDY

To study the correlation of liver stiffness measurement and development of Hepatocellular Carcinoma.

REVIEW OF LITERATURE

Worldwide, in terms of cancer-related deaths liver cancers are the fourth most common cause and rank sixth in terms of incident cases.[1,2] As per an estimate by the World Health organization more than 1 million patients will die from liver cancer in 2030[1]. Liver cancers have 18% 5-year survival, and is the second most lethal tumor, after pancreatic cancer.[1]

RISK FACTORS

More than 90% cases of HCC occur in the setting of chronic liver disease, therefore making it the strongest risk factor for HCC.[20,21] The annual incidence of HCC is 1-6% and is the leading cause of death in patients of cirrhosis.[22] This risk varies according to cause, geographic area, sex, age, and degree of liver damage. Worldwide HBV is the main cause of HCC, whereas in western countries and Japan HCV in the main cause.[1] Other causes include HCV, Dietary exposure to aflatoxin B1 amplifies risk of HCC in HBV infection, NAFLD, NASH, Alcoholic cirrhosis, smoking, inborn errors of Metabolism, primary biliary cholangitis.[23]

WORLD EPIDEMIOLOGY

Most of the burden of liver cancer is in developing countries, where almost 85% of the cases occur. Globally, most of the cases of HCC (>80%) occur in sub-Saharan Africa and in Eastern Asia, with typical incidence rates of more than 20 per 100,000 individuals.[24] Southern European countries (such as Spain, Italy, and Greece) have a mid-incidence rate (10-20 per 100,000 people), whereas HCC is rare in North America, South America, Northern Europe, and Oceania (5.0 per 100,000 people).[24] Recent reports indicate that the incidence of HCC is also decreasing in Chinese populations in Hong Kong, Shanghai, and Singapore; the incidence in Japan is also decreasing.[24] Except in populations where HBV infection is hyper endemic, HCC is rarely seen during the first 4 decades of life.[24] The mean ages of diagnosis with

HCC were 63-65 years in Europe and North America and 55-59 years in China. In low-risk populations, the highest incidence of HCC is among individuals aged 75 or older. HCC is predominant among men, with the highest male: female ratios in areas of high incidence that is South Korea (4.1), North Korea (4.1), Vietnam (4.1), Indonesia (4.3) and France (4.8).[24]

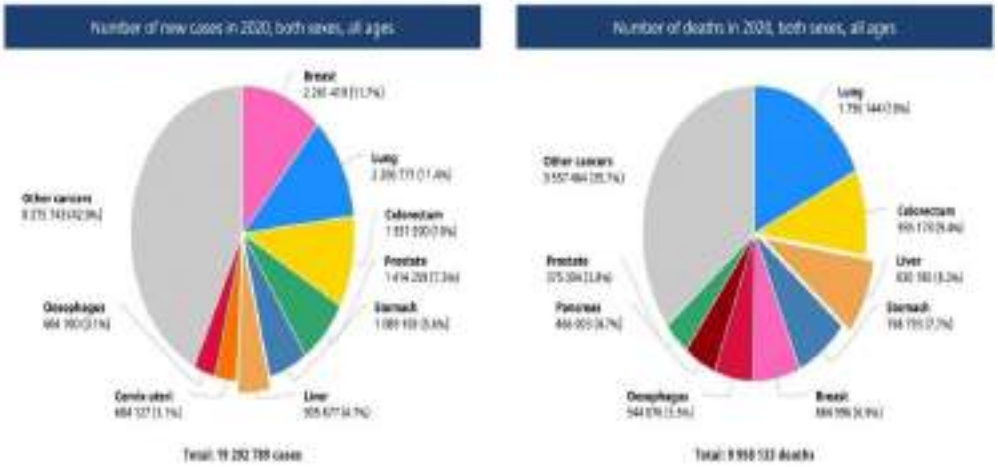

Figure 1: Cancer Incidence and Mortality (Worldwide epidemiology of Liver Cancer in 2020). [25]

Figure 2: Region wise Cancer Incidence, Mortality and Prevalence (Worldwide epidemiology of Liver Cancer in 2020)[25].

Cancer incidence and mortality statistics worldwide and by region

	Incidence						Mortality					
	Both sexes		Males		Females		Both sexes		Males		Females	
	New cases	Cum. risk 0-74 (%)	New cases	Cum. risk 0-74 (%)	New cases	Cum. risk 0-74 (%)	Deaths	Cum. risk 0-74 (%)	Deaths	Cum. risk 0-74 (%)	Deaths	Cum. risk 0-74 (%)
Eastern Africa	12 336	8.55	7 228	0.68	5 109	0.44	11 342	0.54	6 718	0.66	4 624	0.43
Middle Africa	6 872	8.64	4 284	0.80	2 588	0.49	5 716	0.62	3 956	0.88	1 758	0.39
Northern Africa	31 915	1.65	20 468	2.40	11 445	1.28	18 952	1.75	11 408	2.30	6 544	1.22
Southern Africa	2 661	8.02	1 626	0.72	975	0.32	2 447	0.68	1 574	0.72	873	0.29
Western Africa	17 635	8.98	11 678	1.29	6 011	0.62	16 887	0.92	11 384	1.26	5 503	0.62
Caribbean	3 363	8.43	1 908	0.76	1 455	0.47	3 162	0.77	1 888	0.72	1 274	0.44
Central America	11 810	8.72	5 895	0.76	5 528	0.66	11 231	0.69	5 584	0.74	5 647	0.64
South America	24 292	8.49	13 662	0.83	10 631	0.57	23 152	0.67	12 963	0.80	10 198	0.55
Northern America	46 599	8.85	32 505	1.38	14 094	0.65	36 818	0.58	25 321	0.81	11 797	0.33
Eastern Asia	409 887	2.03	307 282	3.04	134 395	1.02	449 634	1.03	326 983	2.75	122 651	0.91
South-Eastern Asia	99 265	1.55	71 696	2.34	27 569	0.79	95 668	1.04	69 984	2.32	26 684	0.75
South Central Asia	54 898	0.95	36 270	0.48	18 485	0.23	52 769	0.55	34 973	0.47	17 796	0.22
Western Asia	11 342	8.55	6 998	0.74	4 344	0.37	10 927	0.53	6 737	0.71	4 190	0.36
Central and Eastern Europe	24 782	8.52	15 184	0.82	9 598	0.38	23 802	0.48	15 885	0.75	9 017	0.28
Western Europe	26 128	8.67	18 598	1.08	7 622	0.29	23 957	0.54	16 620	0.84	7 337	0.26
Southern Europe	24 796	8.80	16 908	1.26	7 858	0.37	21 343	0.59	14 640	0.84	6 707	0.27
Northern Europe	11 914	8.58	7 451	0.81	4 473	0.36	10 513	0.45	6 493	0.63	4 028	0.28
Australia and New Zealand	3 344	8.73	2 429	1.16	915	0.32	2 503	0.48	1 715	0.71	798	0.25
Melanesia	833	1.20	572	1.50	261	1.00	811	1.29	560	1.57	251	1.05
Polynesia	58	8.06	41	1.33	17	0.49	55	0.91	38	1.44	17	0.59
Micronesia	84	1.75	58	2.09	26	0.66	70	1.47	54	2.29	16	0.65
Low HDI	33 997	8.69	20 742	0.91	12 255	0.59	31 662	0.68	19 756	0.90	11 846	0.40
Medium HDI	99 994	8.55	69 168	0.78	30 814	0.33	95 859	0.54	66 358	0.75	29 501	0.32
High HDI	548 935	1.62	391 686	2.48	157 249	0.86	524 867	1.16	373 738	2.30	150 569	0.83
Very High HDI	233 331	8.84	156 489	1.29	72 832	0.43	178 107	0.59	117 470	0.91	60 627	0.31
World	905 677	1.13	622 328	1.65	273 357	0.69	830 180	1.01	577 522	1.49	252 658	0.91

Figure 3: Cancer incidence and mortality statistics worldwide and by region[25]

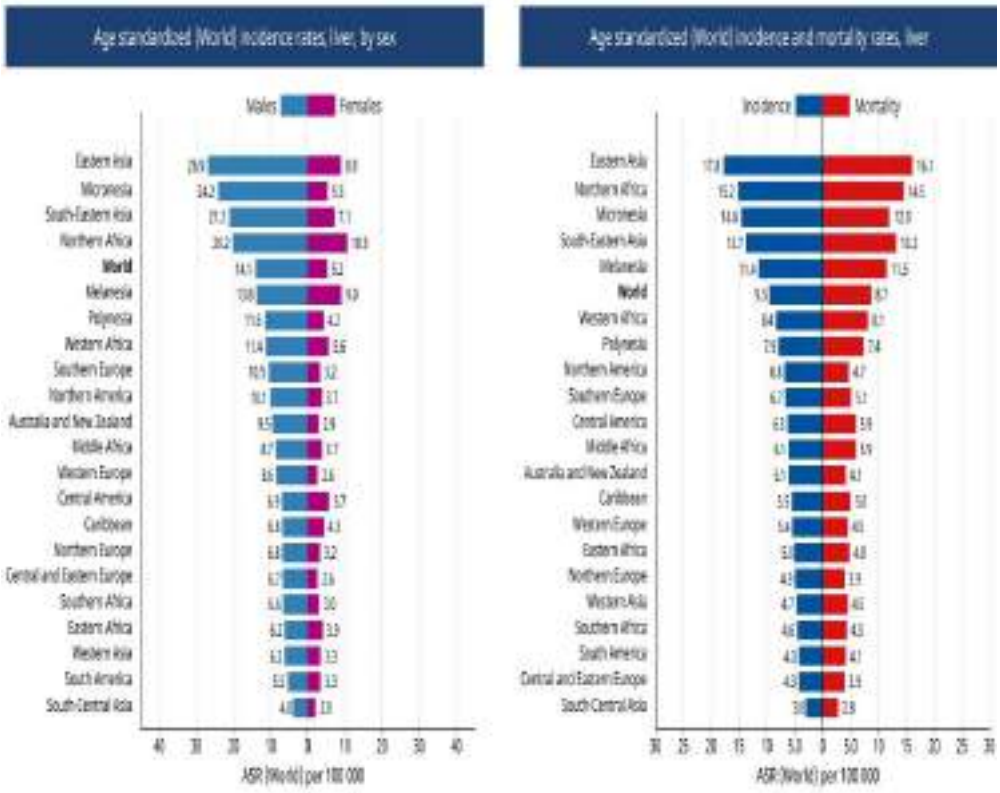

Figure 4: Age standardized Incidence and Mortality of Liver Cancer (Worldwide epidemiology of Liver Cancer in 2020) [25]

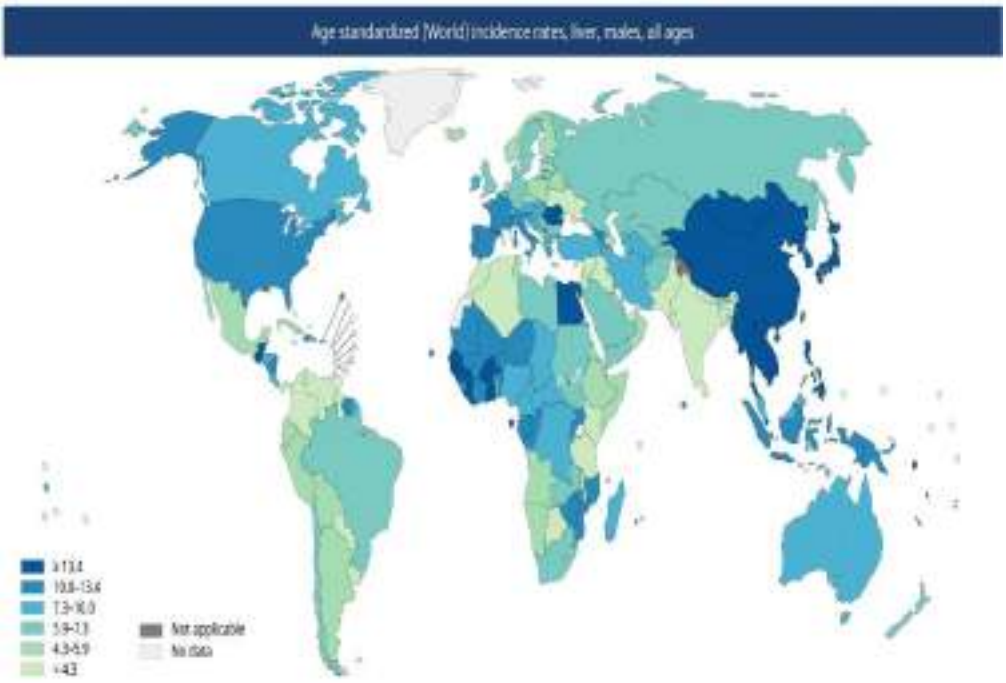

Figure 5: Age Standardized Incidence of Liver cancer among male (Worldwide epidemiology of Liver Cancer in 2020)[25]

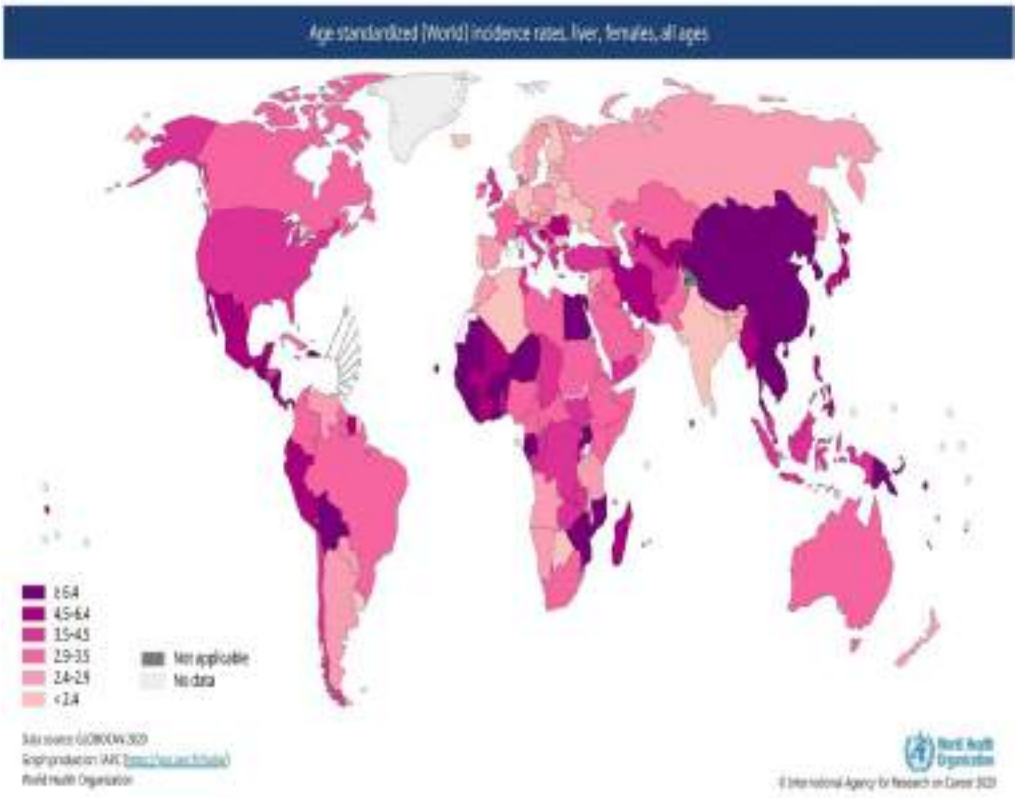

Figure 6: Age Standardized Incidence of Liver cancer among female (Worldwide epidemiology of Liver Cancer in 2020) [25]

INDIAN EPIDEMIOLOGY

In India, information on HCC is inadequate; whatever information comes about the incidence of HCC comes from autopsy data, cancer registries and population based surveillance data.[26,27] Data whatever is present is sparse and of variable and uncertain quality. The incidence of HCC as reported by various population-based registries across the country show a marked (>30-fold) variation in crude and age-adjusted incidence rates of HCC. The crude incidence rate of HCC in India in the year 2015 was 2.8 cases per 100,000 population per year (males: 3.9, females: 1.6), and the crude mortality rate was 2.7 per 100,000 population per year.[28]

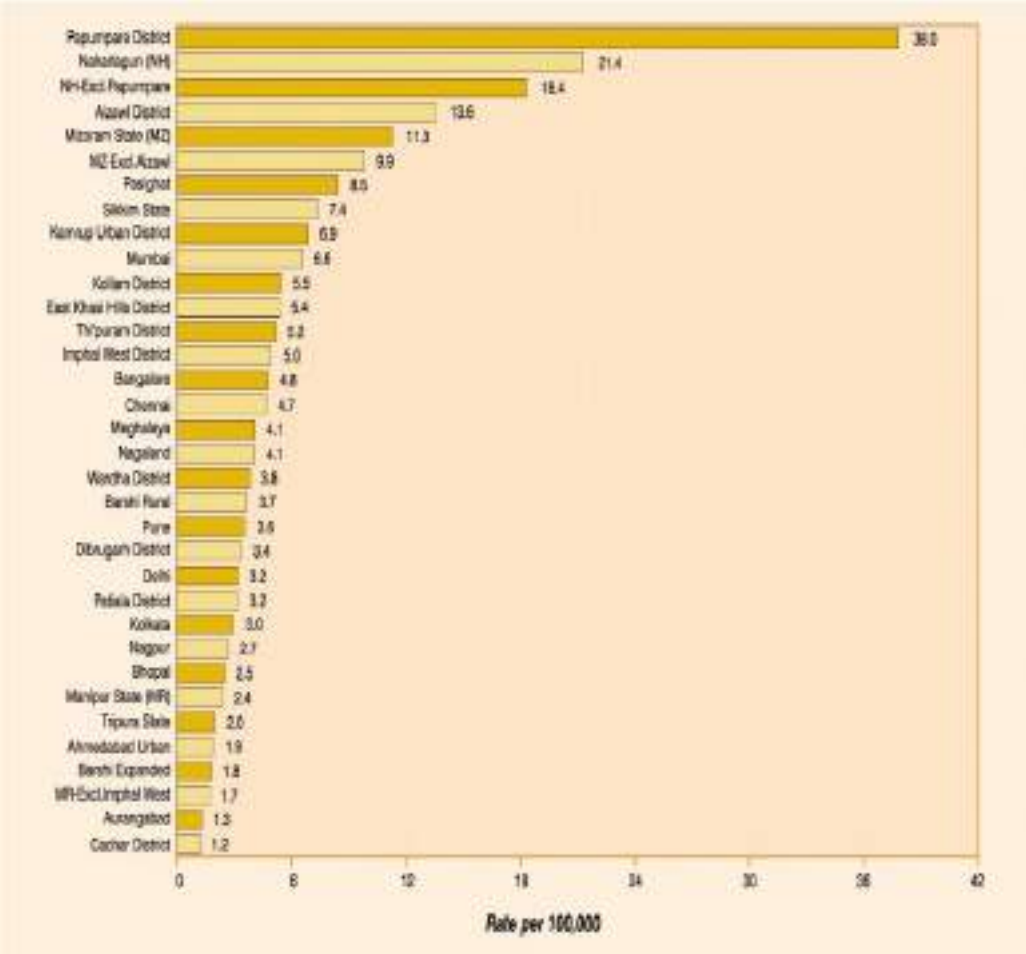

Figure 7: Comparison of Age Adjusted Incidence Rates (AARs) of All PBCRs LIVER (ICD-10: C22) – Males [28]

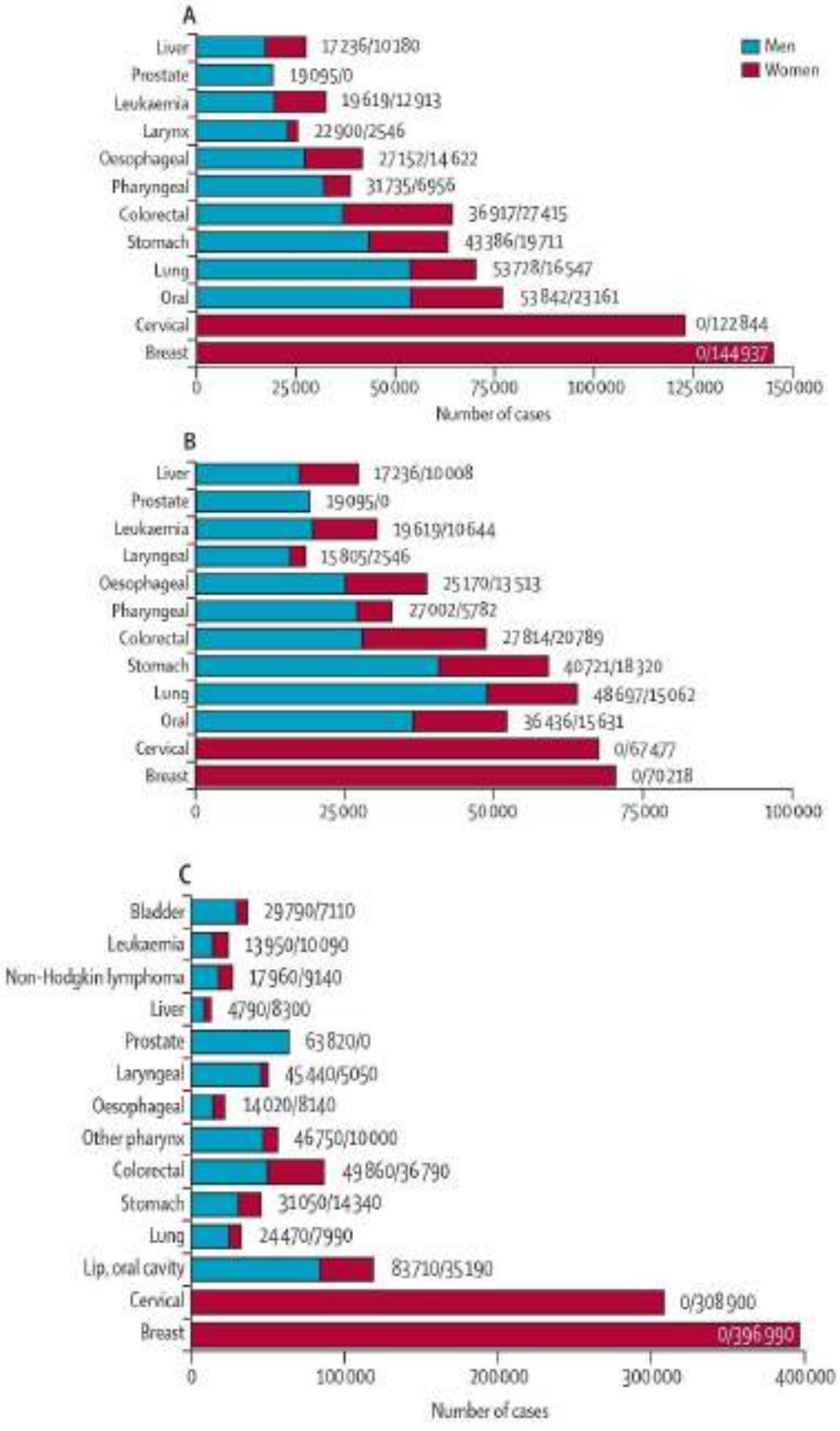

Figure 8: Incidence (A), mortality (B), and prevalence (C) of the most common cancers in Indian men and women in 2012(Data from GLOBOCAN, 2012). [29]

As per a report by The International Agency for Research on Cancer GLOBOCAN project it has been predicted that India's cancer burden will nearly double in the next 20 years, from slightly over a million new cases in 2012 to more than 1·7 million by 2035.[29,30]

Thus from the available data, the conclusion is that the age adjusted incidence rate of HCC in India for men ranges from 0.7 to 7.5 and for women 0.2 to 2.2 per 100,000 population per year. In India, the annual incidence of HCC in chronic liver disease patients is 1.6 percent. The male:female ratio HCC in India is 4:1. The presenting age can be from 40 to 70 years. For men the age standardized mortality rate for Hepatocellular carcinoma in India is 6.8/100,000 and for women it is 5.1/100,000.[26]

Molecular Pathogenesis

Inflammation of hepatocytes, fibrosis, and abnormal regeneration of hepatocytes all occur in patients with CLD, and over time, this can lead to increasing disruption of hepatic architecture, which can lead to cirrhosis.[1,3] Cirrhosis is a premalignant lesion for HCC and additionally there can be a series of genetic and epigenetic events that can result in formation of dysplastic nodules; and these additional molecular alteration favor proliferative, invasive and survival advantages to dysplastic nodules resulting in full blown Hepatocellular carcinoma.[1]

Dysplastic cells accumulate somatic DNA alteration among which *TERT* promotor is the most frequent genetic alteration(60%) and is a recurrent insertion site for the genome of HBV.[31] Other mutations include, mutations affecting the cell cycle (T53) which accounts 30% of cases, WNT signaling pathway (CTNNB1 and AXIN1) accounts 30% and 10% cases respectively and chromatic remodelling (ARID1A and ARID2) which accounts 10% and 5% cases respectively.

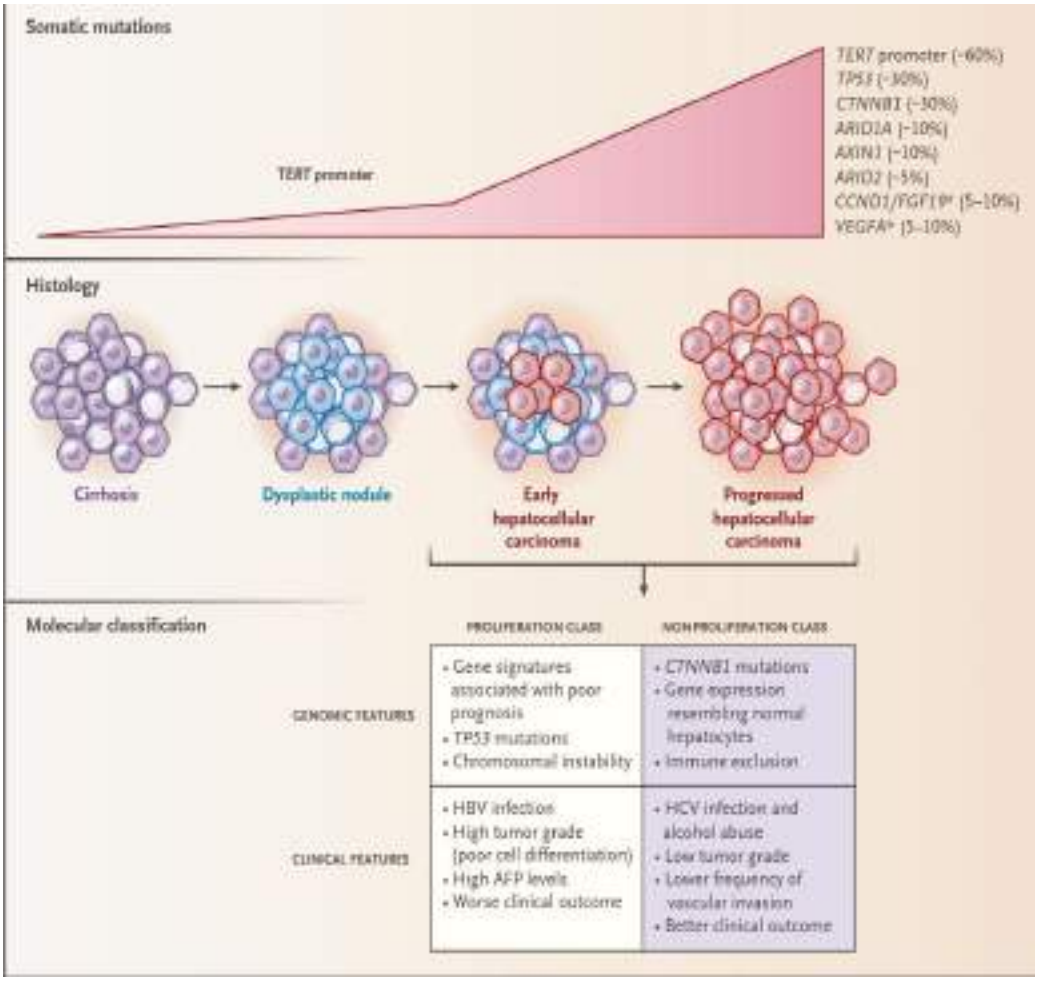

Figure 9:Main Genetic alterations in HCC and Molecular classification[1]

Screening

The aim of surveillance is to detect cancer at early stages and gives an opportunity to use curative treatments and improve survival. As per a randomized controlled study in China among 17,920 persons with HBV infections, it was shown that HCC-related mortality decreased by 37% in compared to patients not screened for HCC.[32]

As per guidelines issued by scientific societies it is recommended that screening for HCC should be performed 6 monthly as it improved survival as compared to annual surveillance and non-inferior outcomes as compared with a 3-month survival interval.[33]

Patient population*	Expected incidence per population	Threshold incidence for cost-effectiveness
Cirrhosis from any aetiology, Child-Pugh A or B		
Hepatitis B cirrhosis	3–8% per year	0.2–1.5%
Hepatitis C cirrhosis	3–5% per year	1.5%
Alcohol-related cirrhosis	1.3–3% per year	1.5%
NASH cirrhosis	Unknown, but probably 1–2% per year	1.5%
Haemochromatosis and cirrhosis	Unknown, but probably >1.5% per year	1.5%
α1 antitrypsin deficiency and cirrhosis	Unknown, but probably >1.5% per year	1.5%
Stage 4 primary biliary cirrhosis	3–5% per year	1.5%
Other cirrhosis	Unknown	1.5%
Non-cirrhotic hepatitis B		
Asian male hepatitis B carriers >40 years	0.4–0.6% per year	0.2%
Asian female hepatitis B carriers >50 years	0.3–0.6% per year	0.2%
Hepatitis B carrier with family history of HCC	Incidence higher than without family history	0.2%
African Black people with hepatitis B	HCC occurs at a younger age (<40 years)	0.2%
Patients with sufficient risk by risk score such as PAGE-B	>3% cumulative 5-year incidence if score >10	0.2%
Other causes		
Patients with NASH in the absence of cirrhosis	<1.5% per year	1.5%
Hepatitis C infection without cirrhosis (including F3)	<1.5% per year	1.5%

Figure 10:Screening recommended in population groups[21]

Patients with cirrhosis, regardless of the cause, are the target population for surveillance. Surveillance is not appropriate for patients with cirrhosis and severe liver dysfunction who are not candidates for curative treatment.

Currently Abdominal USG is the recommended method for surveillance which is done every 6 monthly, with or without measurements of serum levels of alpha-fetoproteins. Since USG is an operator dependent modality the sensitivity of the modality is of 47 to 84% and a specificity of more than 90%.[34]

Recently Mutation analysis of circulating tumour DNA (Liquid biopsy) has been emerging as a new tool for early detection of HCC but its performance is yet to be established.[35-40]

Clinical Guidelines for surveillance of HCC

American Association for the Study of Liver Diseases (AASLD)

Indication

- Cirrhosis; Child-Pugh class A, class B
- Cirrhosis; Child-Pugh class C; eligible for livertransplant
- High risk individuals with hepatitis B:
  - Asian men age >40
  - Asian women age >50
  - Family history of hepatocellular carcinoma
  - Black race

Surveillance test

- Abdominal ultrasonography with or without alpha fetoprotein
- Magnetic resonance imaging (MRI)/computed tomography (CT) can be used for patients with a high likelihood of having inadequate ultrasonography

Surveillance interval

- Everysixmonths

European Association forthe Study of the Liver (EASL)

Indication

- Cirrhosis; Child-Pugh class A, class B
- Cirrhosis; Child-Pugh class C; awaiting liver transplant
- Patients without cirrhosis who have hepatitis B at intermediate or high risk of Hepatocellular carcinoma according to PAGE-B classes for white individuals
- Patients without cirrhosis who have stage 3 liver fibrosis (F3) based on individual risk assessment

Surveillance test

- Abdominal ultrasonography
- alpha fetoprotein is not recommended particularly in patients with active liver inflammation

- MRI/CTcan be used for patients on the waiting list for liver transplant
- MRI/CT can be used for patients who have had inadequate ultrasonography, but risk and cost make their use in long term surveillance highly debatable

Surveillance interval

- Every six months

Asian Pacific Association for the Study ofthe Liver (APASL)

Indication

- Cirrhosis; Child-Pugh class A, class B
- Cirrhosis; Child-Pugh class C; eligible for liver transplant
- High risk individuals with hepatitis B:
  - Asian men age >40
  - Asian women age >50
  - Family history of hepatocellular carcinoma
  - Black race age >20

Surveillance test

- Abdominal ultrasonography with or without alpha fetoprotein

O Cut-off value alpha fetoprotein should be set at 200 ng/mL for surveillance programs when used in combination with ultrasonography

O Cut-off value alpha fetoprotein can be set at lowe value with hepatitis virus suppression or eradication

Surveillance interval

- Every six months

Various mathematical models, Clinical trials, cohort studies and meta-analysis all show survival benefits of surveillance and this evidence substantiates the recommmendation of surveillance by major hepatology professional societies.[20-21,41]

Diagnosis

In patients with cirrhosis, HCC can be diagnosed with the use of imaging techniques because of vascular shift that occurs during malignant transformation of hepatocytes, in which benign lesions (e.g. regenerative and dysplastic nodules) are supplied by branches of the portal system, whereas malignant nodules are supplied from the hepatic artery.[42] This shift translates into a distinctive pattern of hyper enhancement in the arterial phase and washout in venous or delayed phases on contrast-enhanced CT or MRI. This pattern has a sensitivity between 66% and 82% and a specificity higher than 90% for the diagnosis of HCC in patients with cirrhosis and nodules larger than 1 cm in diameter.[43] These hepatic nodules on the basis of the likelihood they represent HCC are reported by Liver Imaging reporting and Data System.[44] These lesions are classified into five categories based on APHE, size, portal venous or delayed washout, threshold growth, and capsule appearance. LI-RADS 1 and LI-RADS 2 classify lesions that are definitely benign and probably benign, respectively, and can be monitored under regular surveillance. LI-RADS 3 indicates a low probability of HCC and it is recommended that repeat imaging be performed after 3 to 6 months. LI-RADS 4 indicates probable but not definite HCC, and multidisciplinary discussion is recommended with biopsies or repeat or alternative imaging within 3 months. LI-RADS 5 indicates definite HCC.

Diagnosis of Hepatocellular carcinoma

American Association for the Study of Liver Diseases (AASLD)

Radiologic test

- Multiphase CT
- Multiphase MRI

Non-invasive diagnostic criteria

- Lesion ≥2 cm in diameter: Non-rim APHE; and non-peripheral washout, enhancing capsule, or threshold growth
- Lesion 1-2 cm in diameter: Non-rim APHE; and non-peripheral washout or threshold growth

Histological diagnosis

- Consider biopsy of LI-RADS 4 or LI-RADS M lesion

European Association for the Study of the Liver (EASL)

Radiologic test

- Multiphase CT
- Multiphase MRI
- Contrast enhanced ultrasonography

Non-invasive diagnostic criteria

- Lesion ≥1 cm
  - APHE and portal venous or delayed washout on multiphasic CT or MRI
  - APHE and mild washout after 60 seconds on contrast enhanced ultrasonography

Histological diagnosis

- Biopsy of >1 cm in diameter, indeterminate lesions on CT, MRI, or contrast enhanced ultrasonography

Asian Pacific Association for the Study of the Liver(APASL)

Radiologic test

- Multiphase CT
- Multiphase MRI
- Contrast enhanced ultrasonography

Non-invasive diagnostic criteria

- Lesion ≥1 cm in diameter
  - APHE and portal venous or delayed washout on multiphasic CT or MRI
  - APHE and hypointensity in hepatobiliary phase (gadoxetate disodium(Eovist) MRI)
  - APHE and defectin the Kupfferphase on contrast enhanced ultrasonography

Histological diagnosis

- Biopsy of >1 cm in diameter indeterminate lesions on CT, MRI, or contrast enhanced ultrasonography

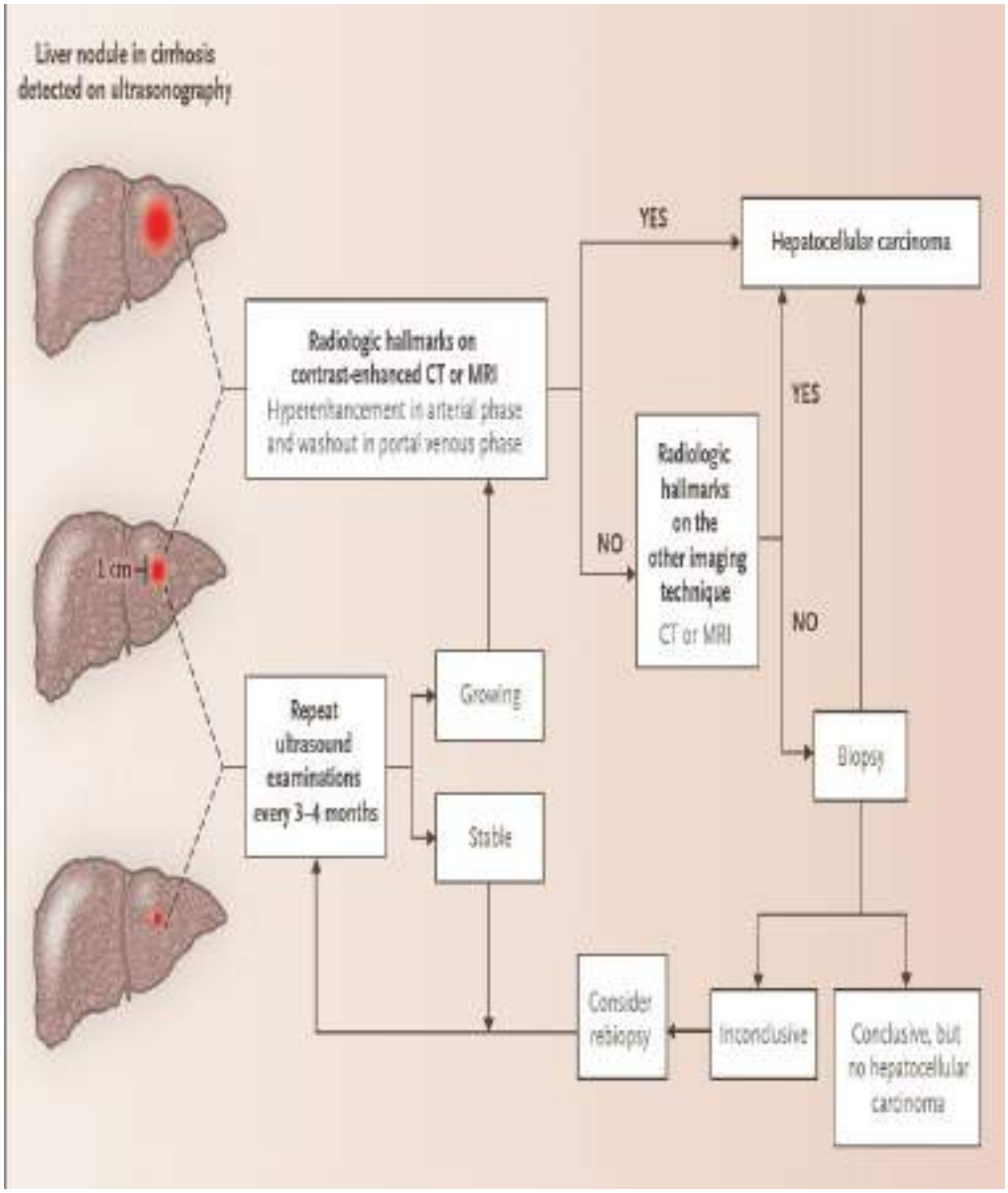

Figure 11: Diagnostic Algorithm for a liver nodule in a patient with Cirrhosis[1]

Contrast enhanced ultrasonography is also used to characterize liver nodules, and is currently used as a diagnostic modality in various centers at Europe[20] and Asia[41] but its precise diagnostic role is still under investigation. There are some nodules during imaging which

have an inconclusive pattern, such patients should rely on biopsy. However, some nodules are very small and histological diagnosis in these patients can be challenging, but a set of immunostaining markers- Glypigan 3, heat shock protein 70, and glutamine synthetase can increase the diagnostic accuracy.[45]

FibroScan® (FS) (Echosens, Paris, France)

Transient elastography (TE) is a new non-invasive tool for measuring liver stiffness, which is correlated to the histological stage of liver fibrosis[46] has been widely validated in assessment of liver fibrosis.[47]It has range of 3 probes (S+, M+ and XL+) designed to fit the patient morphology, the prototype of fibroscan comes with the regular sized probe, the M probe. As many as 40 studies which included over 7700 patients all over the world has validated the use of LSM by M probe.[48]

Table 1: Comparison of Fibroscan probe

FibroScan® S+ Probe	**FibroScan® M+ Probe**	**FibroScan® XL+ Probe**
For thin patient Designated for being placed into narrow intercostal space	For standard morphotype's patients	For overweight patients Designed to enhance signal penetration through deeper tissues
Measurement depth From 15 to 50 mm	**Measurement depth** From 25 to 65 mm From 25 to 70 mm with smart exam	**Measurement depth** From 15 to 50 mm From 35 to 85 mm with smart exam
Criteria of selection Age < 18 yrs And Thoracic perimeter≤ 75 cm	**Criteria of selection** Age < 18 yrs And Thoracic perimeter ≤ 75 cm Or Age ≥ 18 yrs And no XL+ probe recommendation	**Criteria of selection** Age ≥ 18 yrs And no M+ probe recommendation

LSM is an accurate and reproducible method to predict advanced liver fibrosis and cirrhosis in various chronic liver disease.[49-51]

Liver stiffness is defined as the median of 10 successful measurements and according to the manufacturer's recommendations at least 60% of the shots should be successful measurements and according to the manufacturer's recommendations at least 60% of the shots should be successful for each exam. The validity of the results depends on one important parameter: the variability of measurements. This is reflected by the inter quartile range (IQR), representing the range of values including 50% of patients above and below the median. According to the manufacturer's suggestion IQR/median stiffness ratio should not exceed 30% of the median value. In one of the study it was observed that IQR/median stiffness ratio below 20% gave the best concordance between liver biopsy and transient elastography.[52]

Normal liver stiffness ranges between 3.3-7.8 kPa and using a cut off of 7.1 Kpa, a significant fibrosis and cirrhosis can be excluded with a very high negative predictive value (NPV).[53] Many studies have been published on CLD patients but only 3 studies (Roulot D. et al[54], Corpechot C. et al[55] and Colombo S. et al[56] are there in apparently normal subjects.

Table2: Recommended values for different stage of fibrosis[57]

Disease	F0–F1 (Kpa)	F2 (Kpa)	F3 (kpa)	F4 (kpa)
Hepatitis B	≤6.0	≥6.0	≥9.0	≥12.0
Hepatitis C	≤7.0	≥7.0	≥9.5	≥12.0
HCV–HIV coinfection	≤7.0	≤10	≥11.0	≥14.0
Cholestatic liver disease	≤7.0	≥7.5	≥10.0	≥17.0
NAFLD/NASH	≤7.0	≥7.5	≤10	≥14.0

Pathophysiology of liver stiffness

Liver stiffness – definition

From a physical and mechanical point of view, Liver stiffness can be defined as the modulus of elasticity or Young's modulus (E).Hooke's law of elasticity is an approximation that states that the extension of a material is directly proportional to the applied stress, $\sigma = E\varepsilon$, where σ is the stress applied to the material, and ε is the strain induced in the material. Stiffness (E) is expressed in kilopascals (kPa) and represents the resistance of material to deformation. While stiff materials, such as concrete, exhibit low strain even at high stress, soft materials such as biological soft tissues exhibit large strain even at low stress.

Stiffness of liver depends upon many factors; the first and main factor is the extracellular matrix of the organ which is a deformable structure that transfers the external forces through the liver. The second factor is the constraints that are applied on the organ. The more pressure that is applied to the liver at its boundaries, the stiffer it gets. The internal pressure inside the organ – if blood or another liquid is coming in and out is the third factor, then stiffness will depend on the resistance that the organ applies to the flow. The fourth and important factor is the viscous effects which influence the time constant over which stiffness is tested. This effect is linked to frequency that is stiffness depends on frequency. While liver is soft at very low frequency (on the order of several hertz) which corresponds to manual palpation time-constant, it tends to be much harder at high frequencies (over several tens of kilohertz).

Measurement of liver stiffness using transient elastography (FibroScan®)

The FibroScan® (FS) device (Echosens, Paris, France) is the first elastography tool created to test soft biological tissue stiffness in vivo quantitatively and noninvasively. Because of its size and uniform texture, the liver was the first organ to be investigated.[58] Shear waves

are created in theory via the liver, and their velocity is used to calculate Liver Stiffness. Transient elastography (TE) or vibration-controlled transient elastography (VCTETM) is a technology used by Fibroscan. It is based on the controlled creation of a transient shear wave with a defined frequency and amplitude utilizing a servo-controlled vibration. Liver Stiffness is computed from the velocity of these mechanical waves using the following equation:

$E = 3\rho Vs^2$

Where E is the Young's modulus or stiffness, ρ is the density, and Vs the shear velocity. VCTETM measures a group velocity of roughly 50 Hz for shear velocity. Fibroscan can measure minimum and maximum stiffness values of 1.5 kPa and 75.0 kPa, respectively. Fibroscan is a dedicated acquisition platform that contains a single channel ultrasound analogue, the front end is for emitting and receiving ultrasound signals, as well as a servo controlled vibrator for generating shear waves. The probe itself has a sophisticated vibrator with a single element ultrasonic transducer positioned on its axis. The vibration has a sinusoidal period with a 50 Hz center frequency. The amplitude varies depending on the probe model: 2 mm peak-to-peak (PP) with the regular probe (model M), 1 mm PP with the pediatric probe (model S), and 3 mm PP with the customized probe for obese patients (model S) (model XL). Ultrafast ultrasonic acquisitions are used to track the propagation of shear waves. Liver stiffness using Fibroscan is conducted on the right lobe of the liver in the intercostal position in normal testing methods. This prevents direct compression of the liver, which would alter Liver stiffness measurements. The patient is lying on his back with his right arm behind his head to maximize intercostal space. The operator uses ultrasound M-mode and A-mode images to locate the liver, and triggers the measurement by pushing on the probe button. On the elastogram image, which shows the strains caused in the liver as a function of time and depth, the shear wave can be seen. It is calculated using ultrasonic data acquired at a very high frame rate during the 80-ms shear wave propagation.

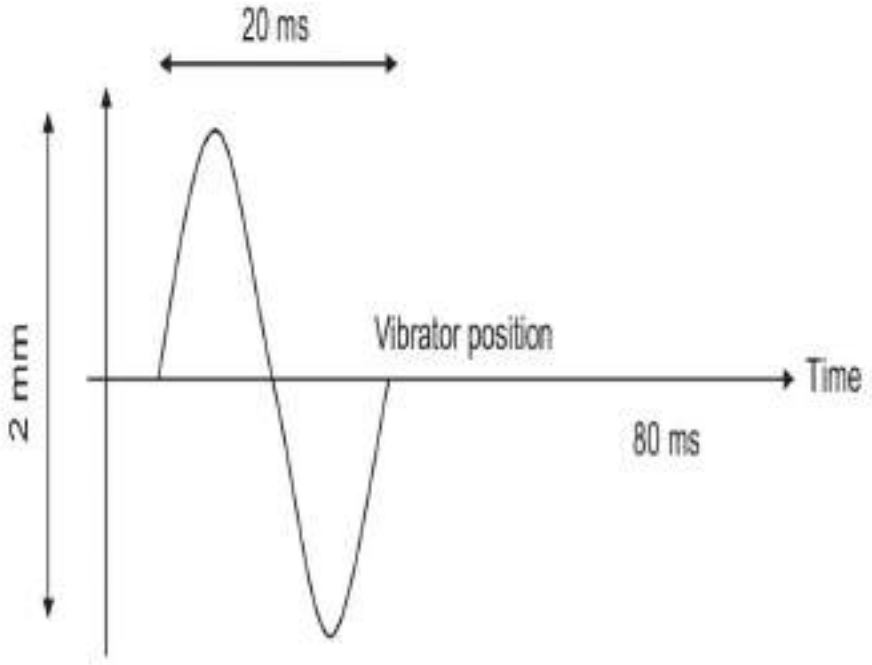

Figure 12: FibroScan® vibration consists of a period with a center frequency of 50 Hz. The standard M probe has a 2 mm peak-to-peak amplitude.[59]

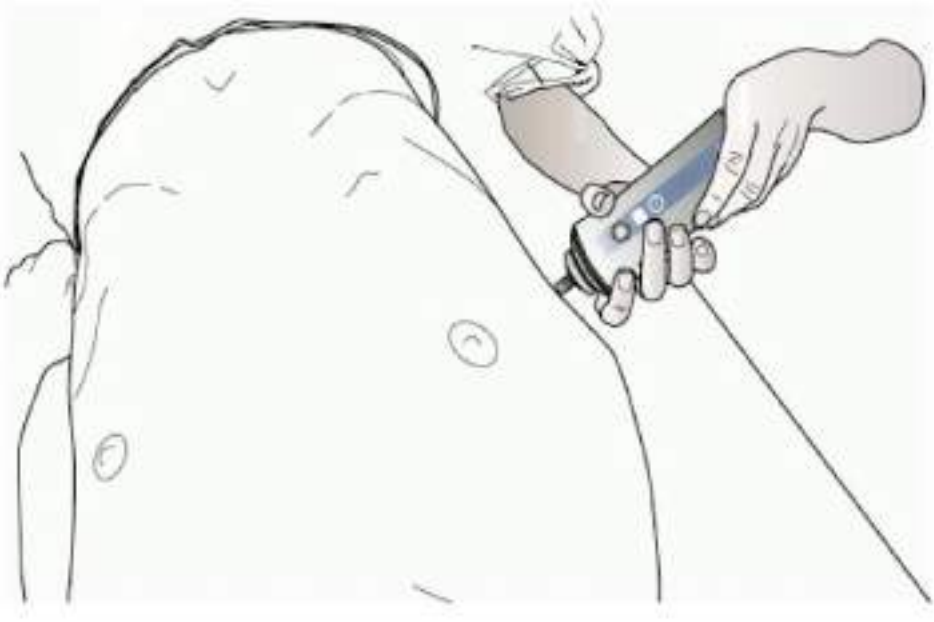

Figure 13: Liver stiffness measurements are performed on the right lobe of the liver in intercostal position using FibroScan®.[59]

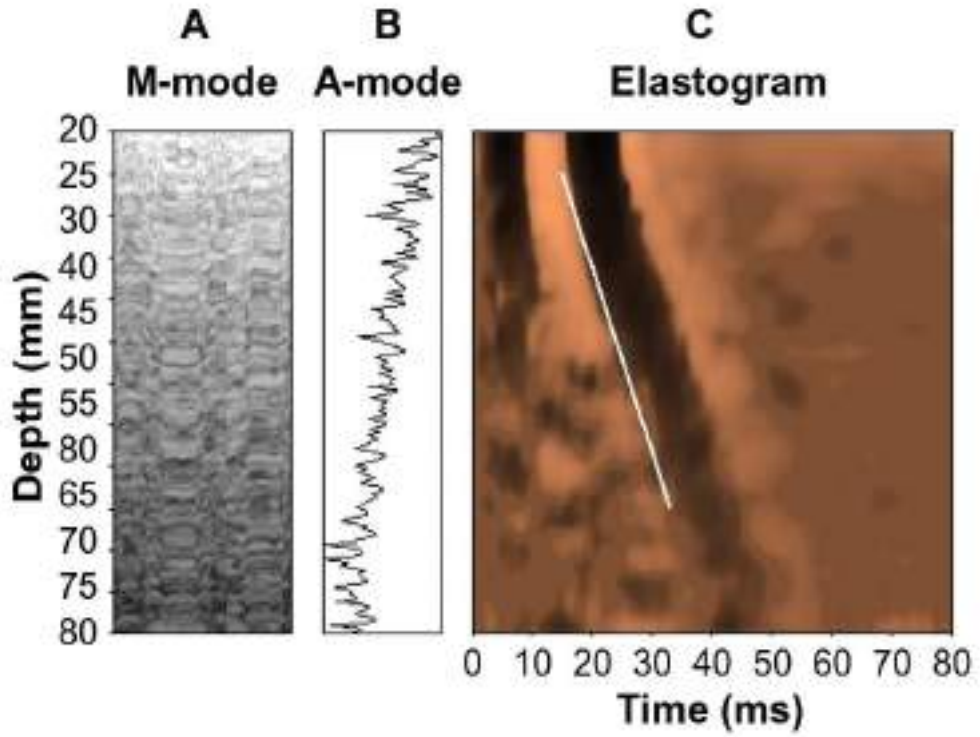

Figure 14:FibroScan® operator uses A) A-mode and B) M-mode images to locate the liver. The shear wave velocity is deduced from the C) elastogram which represents the strains induced in the liver by the shear wave propagation as a function of time and depth.[59]

Clinical applications of Transient Elastography

1) **Pre-treatment assessment of liver fibrosis**

The severity of liver fibrosis is the key factor of timing and choice of therapy. Current guidelines recommend antiviral therapy for CHB patients with significant liver fibrosis.[60-62]

2) **Follow-up assessment of liver fibrosis**

A few longitudinal studies have reported that treatment had low or decreased liver stiffness.[63] It has been studied that the reduction in liver stiffness is contributed to both the reduction in fibrosis and necroinflammation.[64] Verginol et al studied 416 patients of whom 112 started treatment after enrolment. In multivariate analysis, treatment

was the only factor independently associated with a fall in Liver stiffness.[65] In a prospective study of 145 Japanese patients with chronic HCV infection, Ogawa et al found that liver stiffness was significantly reduced in the groups with sustained virological and biochemical responses, but not in non responders, at baseline, at the end of treatment, and at 48 and 96 weeks after treatment.[66] Anderson et al in there prospective study of 114 Japanese patients of chronic HCV infection followed up patients for 47-48 months and found that Liver stiffness was significantly lower for patients with sustained viral response(SVR) and the results were more significant in F2-F4 group.[67]

LSM post-SVR could be useful in refining the stratification of residual risk of liver-related problems in patients with advanced compensated chronic liver disease prior to antiviral medication; yearly repetition of LSM can be done while waiting for confirming evidence.[68]

3) **Predict portal hypertension and variceal bleeding**

Liver fibrosis increases the hepatic vascular resistance and ultimately leads to increased portal hypertension. Transient elastography has been demonstrated to be beneficial in identifying cirrhotic patients with a higher risk of portal hypertension, with cutoff values of 17.6 kPa and 21.0 kPa having a sensitivity of 90% in detecting patients with a hepatic venous pressure gradient (HVPG) of 10-12 mm hg.[69-70] Studies have compared liver stiffness directly with the presence of esophageal varices in adults[71-78] and children.[75] Presence of varices can be excluded with a liver stiffness below 12.5-19.8 kPa.[71,76]

4) **Liver stiffness and post-operative outcomes**

As there is limited organ supply it becomes important to quantify risk assessment strategies for patients who will have a better outcome. A prospective study of 105 HCC patients found that an LSM threshold of 12.0 k Pa had a sensitivity of 86% and specificity of 72% in predicting serious post-operative problems, indicating that this cutoff may identify patients who require more transfusions and had more severe surgical

blood loss.[79] Another study of 133 HCC patients revealed that patients of LSM ≥ 13.4 k Pa had a 2-fold increase in the risk of HCC recurrence compared to those with LSM <13.4 k Pa.[80]

5) **Assessment of liver steatosis**

As per epidemiological data Obesity is on rise and this has resulted in liver steatosis which is a common histological feature in the general population and in patients with chronic liver disease. The prevalence is as high as 30% in general population,[81-82] 50% in patients with chronic hepatitis C[83] and above 80% in severely obese patients.[84] Patients with significant grade of liver steatosis are associated with lower response rate to treatment to antiviral treatment[85] and liver fibrosis progression.[86]Liver steatosis may increase the risk of HCC[87] and is an important risk factor for post operative complications and mortality after liver resection.[88]

6) **Prediction of HCC**

Use of TE as for prediction of HCC is promising area of interest among physicians. Unless HCC is diagnosed at an early stage, a poor prognosis is expected due to the limited treatment options.[89-91] Several cross-sectional studies demonstrated that the median value of liver stiffness in patients with HCC are significantly higher than in those without HCC.[92-94] One of the study was conducted by Ryota Mauzaki et al. did a Multivariate analysis and showed that Hepatocellular Carcinoma (HCC) presence was significantly associated with liver stiffness along with other variables age, male, and alpha-fetoprotein concentration. AUROC was 0.805, 0.741, 0.714, 0.673, 0.670 and 0.654 for liver stiffness, alpha-fetoprotein, albumin, pro thrombin activity, AST-platelet ratio index, and platelet count, respectively. They concluded that liver stiffness measured by transient elastography is useful in demarcating chronic hepatitis C patients at a high risk for HCC, who require frequent check-up by imaging examinations.[93]

Many prospective trials have been conducted in the past to study the role of TE in predicting HCC, one of these trial was conducted by

Poynard et al.[94](n= 3927) on chronic hepatitis C patient found that LSM was predictive of severe liver-related complications(AUROC 0.77; P<0.0001), Including primary HCC(AUROC 0.86; P<0.0001).

Other authors tried to quantify with LSM the risk of developing HCC after antiviral therapy. Rinaldi et al[94] found that an LSM cut-off value of 27.8 kPa at baseline before treatment identified patients at high risk of HCC after DAA, whereas Corma-Gomez et al[95] found in an HIV/HCV cohort treated with DAA that also Fib-4 in addition to LSM was associated with HCC occurrence. Another recent study[96] carried out in patients undergoing antiviral therapy found that baseline LSM>30 kPa independently predicted de novo HCC, with a 3-year estimated incidence of 20% in these patients versus 5% in patients with LSM ≤ 30 kPa.

Most studies only highlighted the 'static' phenomenon, without analyzing the 'dynamic' correlation between the progression or regression of hepatic fibrosis and the risk of developing HCC. The first study to overcome this limitation was conducted by a Japanese group on a large cohort of 866 subjects with chronic hepatitis C[97], and proved that LSM value > 10 kPa is an accurate predictor of increased HCC risk(LSM values 10.1-15 kPa, HR 16.7; LSM 15.1-20, HR 20.9; LSM 20.1-25, HR 25.6; LSM > 25 kPa, HR 45.5, all with P<0.001). In another prospective study by Kyu sik Jung et al.[98] on 1,130 patients with non-biopsy-proven chronic hepatitis B for the role of FibroScan in assessing the degree of liver fibrosis and the risk of development hepatocellular carcinoma concluded that Liver stiffness Measurement could be a useful predictor for Hepatocellular Carcinoma development in patients with Chronic Hepatitis B. They noticed that subjects with LSM > 8kPa had an increased risk of HCC, and that incidence of HCC was directly proportional to LSM values: for LSM 8.1-13 kPa, HR 3.07 (P=0.047); for LSM 13.1-18 kPa, HR 4.68 (P= 0.012); for LSM 18.1-23 kPa, HR 5.55 (P=0.009); for LSM > 23 kPa, HR 6.60 (P=0.004). After a median follow-up of 18 months, a second LSM was made to evaluate if changes over time were related to a variation in HCC risk: Patients with baseline LSM ≤ 13 kPa and follow-up LSM > 13 kPa had a significantly

higher incidence of HCC than those with both values ≤ 13 kPa (P< 0.001); on the contrary, subjects with baseline LSM > 13 kPa who had regression of LSM below 13 kPa during follow up had a significant lower incidence of HCC than those who maintained an LSM value > 13 kPa (P< 0.001). Therefore this study demonstrated that LSM can also be used a dynamic predictor of HCC.

Some other notable studies on TE as a predictor of HCC are, J Foucher et al.[10] in there prospective study showed that transient elastography is an excellent efficient technique for the diagnosis of cirrhosis and its severity. With a cut off value of 17.6 kPa, negative and positive predictive values for the diagnosis of cirrhosis were 92% and 91% respectively. They established the cut off values for complications of cirrhosis, with a negative predictive value of more than 90%. These cut off values were 27.5 kPa for oesophageal varices stage 2/3, 37.5 kPa for cirrhosis Child-Pugh B or C, 49.1 kPa for a past history of ascites, 53.7 kPa for HCC, and 62.7 kPa for oesophageal bleeding. In clinical practice such results could be of major relevance for follow up of patients with severe fibrosis or cirrhosis.

Yinghua Zhang et al.[2] determined a significant association between liver stiffness variation and Hepatocellular Carcinoma development in patients with Chronic Hepatitis B with compensated cirrhosis and suggested that liver stiffness by transient elastography is an effective serial assessment for hepatic disease progression.

Takaaki Izumi et al.[99] concluded that in hepatitis C virus patients, the incidence of Hepatocellular Carcinoma development was significantly higher among those with a combination of Liver stiffness measurement >8.0 kPa and CAP <221 dB/m than among those with other values. They also concluded that in non-alcoholic fatty liver disease patients, the incidence of Hepatocellular Carcinoma development was significantly higher among those with a combination of LSM>5.4kPa and CAP<265 dB/m than among others.

Maciej Adler et al.[3] did a 1yr follow up study of 432 cirrhotic patients with LSM >20kPa and concluded that higher LSM values are associated with higher incidence of Hepatocellular Carcinoma risk.

Pierre Nahon et al.[100] did a case control study and found out that patients with Hepatocellular Carcinoma had higher Liver stiffness Measurement than patients without Hepatocellular Carcinoma[35.3 kPa (22.8-52.6) vs. 19.0 kPa (12.4-29.2), P<0.0001]. They concluded that in patients with Child-Pugh A cirrhosis, a wide range of Liver stiffness measurement is observed according to the cause underlying liver disease and the presence of Hepatocellular Carcinoma is associated with higher values in these patients.

Yuan-hung Kuo et al.[101] demonstrated that Liver stiffness measurement was an independent factor in the prediction of Hepatocellular Carcinoma presence. And the risk of Hepatocellular Carcinoma increased with advancement of cirrhosis. With liver stiffness >24 kPa, the likelihood ratio of Hepatocellular Carcinoma presence was 5.9 for chronic hepatitis patients. The sensitivity and specificity in the prediction of HCC presence was 41.5 and 92.7%, respectively.

Ashraf O. Abdelaziz et al.[102] concluded that progression of Chronic hepatitis C is associated with a decrease in steatosis, particularly toward advanced fibrosis and Hepatocellular Carcinoma. Steatosis reduction less than 237 dB/m is likely to be associated with Hepatocellular Carcinoma.

Takaaki Sugihara et al.[103] did a cross sectional study in residents aged >40 years in Japan and concluded that the combination of controlled attenuation parameter and liver stiffness measurement can be useful in detecting high-risk liver diseases of Hepatocellular Carcinoma out of general population.

Yeon Seok Seo et al.[104] did a cohort study on 381 patients and did a follow up period of 48.1 months. In patients with HCC development, age, proportion of diabetes mellitus, histological fibrosis stage and liver stiffness value were significantly higher than those in patients without.

The cumulative incidence rates of HCC increased significantly in association with elevated Liver stiffness value in 3 stratified groups(LS value ,8, 8-13 and, > 13 kPa; log-rank test, P,0.001), and with higher histological fibrosis stage in 3 stratified groups(F0-2, F3 and F4; log-rank test, P,0.001). On multivariate analysis, along with age, liver stiffness value was an independent predictor of Hepatocellular Carcinoma development.

Mi Na Kim et al.[105] investigated that transient elastography(TE) can identify patients with subclinical cirrhosis(SCC) who are at increased risk of developing Hepatocellular Carcinoma among chronic hepatitis B(CHB) patients without clinical evidence of cirrhosis. They did a prospective study on 2,876 study on chronic hepatitis B patients without clinical cirrhosis. Subclinical cirrhosis was defined as a non-clinical cirrhosis, but with a liver stiffness (LS) value >13 kPa. On multivariate analysis, Subclinical cirrhosis was independently associated with a risk of developing Hepatocellular Carcinoma, regardless of antiviral therapy. Thus they concluded that Transient elastography can identify patients with subclinical cirrhosis who are at increased risk of developing Hepatocellular carcinoma, even when cirrhosis is not clinical apparent.

Mi Young Jeon[106] found a significant association between sub cirrhotic range of liver stiffness value and lower risk of HCC development was identified in patients with clinically evident CHB-related cirrhosis.

Limitations of Transient Elastography

TE has several advantages of being non-invasive, quick, cheap, reliable diagnostic accuracy with excellent inter-observer and intra-observer reliability. However the modality carries some drawbacks as additional space-occupying tissue abnormalities, such as edema and inflammation, cholestasis[107], and congestion[108-110] may interfere with TE, regardless of the degree of fibrosis, because the liver is wrapped in a distensible, but non-elastic envelope (Glisson's capsule).[111]

In patients with viral hepatitis the extent of histological necroinflammatory activity has been shown to influence the TE results, resulting in an overestimation of TE values that increases in parallel with the degree of necroinflammatory score.[112-116]In patients with acute viral hepatitis or CHB a risk of overestimation of TE has been reported in cases of ALT flares.[117-123] Thus in subjects with ALT flare up it is advised for repeat examination once the ALT levels have stabilized. Many studies have been conducted and have investigated that an optimal period(3 to 6 months) for restoration of the reliability of TE values in patients with acute flares.[119,122,124,125] Even mild to moderate elevation in ALT can be associated with higher liver stiffness values. Additionally there can be error in values of TE due to high body mass index (BMI), narrow intercostal space, or ascites.

This study was planned to study the role of Fibroscan as a new modality for predicting the risk of development of HCC in patients at risk.

MATERIALS AND METHODS

7.1 Source of Data

Outdoor patient Department (OPD) and wards of General Medicine and Gastroenterology at Dayanand Medical College and Hospital, Ludhiana.

7.2 METHOD OF COLLECTION OF DATA

Cases and control will be selected on the basis criteria set in Inclusion and Exclusion criteria for the study and Fibroscan will be performed in selected patients.

INCLUSION CRITERIA

GROUP A

1. Cirrhosis of any etiology (Compensated and Decompensated)
2. Diagnosis of HCC on either non invasive criteria for a focal lesion defined by the EASL guidelines or histological evidence
3. Age more than 18 Years

GROUP B inclusion criteria:

- Cirrhosis of any etiology
- Compensated cirrhosis
- No evidence of HCC at the time of inclusion, as assessed by negative ultrasonographic screening or tripahsic CT and MRI (wherever indicated).

EXCLUSION CRITERIA

1. BMI >30 kg/m2
2. ALT > 10 times of upper limit of normal
3. Patient's with associated heart failure
4. Local skin disease at site where Fibroscan probe will be kept
5. Pregnant women and patients with active implantable medical devices

Clinical and Laboratory workup

Detailed history and examination of all the patients was done. Patients were examined for jaundice, hepatic encephalopathy, ascites, variceal bleeding. BMI was calculated in all patients. Detailed respiratory, cardiovascular and Gastro intestinal examination was performed.

Determination of the etiology of chronic liver disease was made using standard diagnostic criteria. Hepatitis C virus (HCV) or Hepatitis B virus(HBV) was diagnosed by serological detection of hepatitis C antibodies and hepatitis B surface antigen, respectively. Alcoholic liver disease was diagnosed in those with consumption of at least 40 gm of alcohol daily for 5 years or more. All other disease were diagnosed as standard recommendations. Patients were enrolled after written informed consent is obtained

Liver stiffness measurement

LSM was performed with FIbroscan (EchoSens) by a single operator distinct from the investigators and blinded to clinical and biological data. Details of the technical description and examination procedure have been described previously. Measurements were performed in the right lobe the liver through intercostal spaces on patients lying in the dorsal decubitus position with the right arm in maximal abduction. The tip of the probe transducer was covered with coupling gel and placed on the skin, between the rib bones at the level of the right lobe of the liver. The operator, assisted by an ultrasonic time-motion image, located at least 6 cm thick free of large vascular structures. After locating the measurement area, the operator pressed the probe button to start an acquisition. Measurement depth was kept between 25 mm and 65 mm below the skin surface. Measurement which had not a correct vibration shape or a correct follow up of the vibration propagation were automatically rejected by the software. Up to 10 successful measurements were performed on each patient. Success rate was calculated as the ratio of the number of successful measurements over the total number of acquisitions. The results were expressed in kilopascal (kPa). Median value of the successful measurements kept as representative of liver stiffness. The whole examination duration took less than 5 minutes, Only liver stiffness measurements obtained with at least five successful measurements and a success rate of at least 30% were considered reliable.

STUDY DURATION

The study will conducted from 1st October 2019 to 31st March 2021.

STUDY DESIGN

The study will constitute 2 groups-

Group A: Patients with cirrhosis and Hepatocellular Carcinoma

Group B: Patients with cirrhosis and no Hepatocellular Carcinoma

STATISTICAL ANALYSIS

Data were described in terms of range; mean ±standard deviation (± SD), frequencies (number of cases) and relative frequencies (percentages) as appropriate. To determine whether the data were normally distributed, a Kolmogorov-Smirnov test was used. Comparison of quantitative variables between the study groups was done using Student t-test and Mann Whitney U test for independent samples for parametric and non-parametric data respectively. For comparing categorical data, Chi square ($\chi 2$) test will be performed and exact test will be used when the expected frequency is less than 5. Receiver operator characteristics (ROC) curve was done, and criterion value was estimated depending on the specificity and sensitivity. Area under curve (AUC) was measured. Logistic regression analysis will be used for analysis of independent factor with the outcome of the patients. A probability value (*p* value) less than 0.05 was considered statistically significant. The stratum-specific likelihood ratio (SSLR) is the probability of a test result within a given range or stratum when the disease is present, divided by the probability of a test result within a given range or stratum when the disease is absent. We determined these risk ratios by means of the formula SSLR = $(x_1/n_1)/(x_0n_0)$, where x_1 is the number of patients in the stratum with HCC, n_1 is the total number with HCC, x_0 is the number of patients in the stratum without HCC, n_0 is the total number of patients without HCC. The 95% confidence of each SSLR was calculated. All statistical calculations were done using (Statistical Package for the Social Science) SPSS 21

version (SPSS Inc., Chicago, IL, USA) statistical program for Microsoft Windows.

DOES THE STUDY REQUIRE ANY INVESTIGATIONS OR INTERVENTIONS TO BE CONDUCTED ON PATIENTS OR OTHER HUMANS OR ANIMALS? IF SO, PLEASE DESCRIBE BRIEFLY.

Yes this study requires FIBROSCAN to be performed on patients with cirrhosis

HAS ETHICAL CLEARANCE BEEN OBTAINED FROM YOUR INSTITUTION IN CASE OF 7.3?

Attached herewith

OBSERVATION AND RESULTS

Table 3: Age distribution of subjects

AGE	No. of cases	Percentage
<50	14	23.3%
51-60	22	36.7%
61-70	20	33.3%
> 70	4	6.7%
Total	60	100.0%

Maximum patients were in age group of 51-60 years (36.7%), 33.3% patients were in age group of 61-70 years, 23.3% patients were in age group of <50 years and 6.7% of patients were in age group of >70 years.

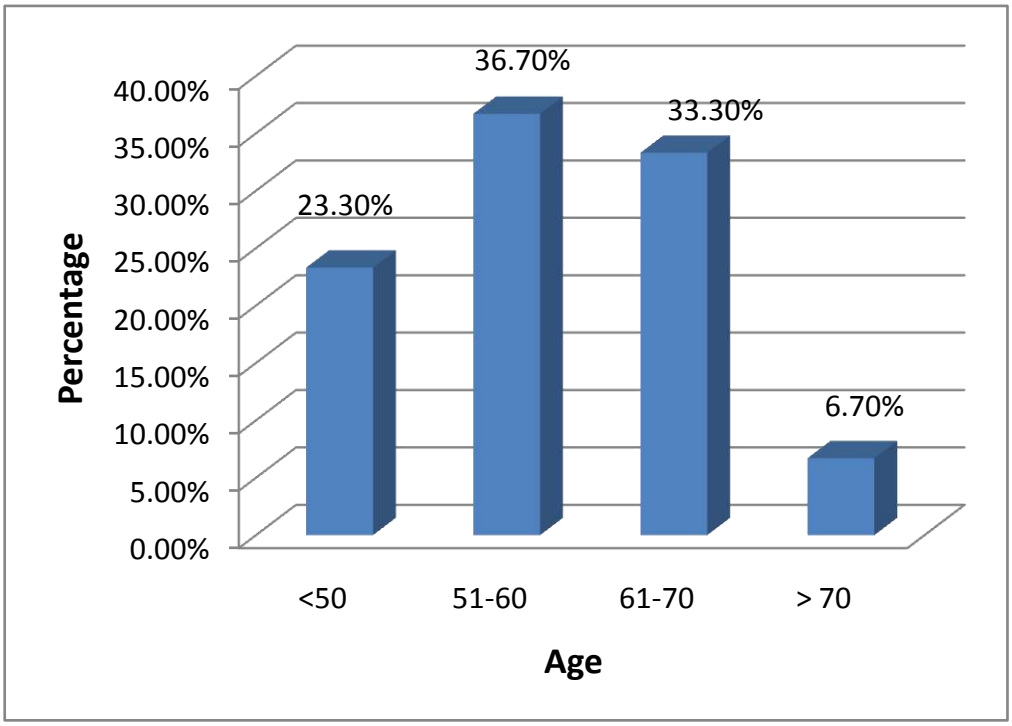

Figure 15 : Age distribution of subjects

Table 4 : Age distribution of subjects in Group A and Group B

		GROUP A		GROUP B		
		No. of cases	%age	No. of cases	%age	Total
AGE	<50	3	10.0%	11	36.7%	14
	51-60	10	33.3%	12	40.0%	22
	61-70	14	46.7%	6	20.0%	20
	>70	3	10.0%	1	3.3%	4
Total		30	100.0%	30	100.0%	60
		Mean	SD	Mean	SD	
	AGE	60.10	8.14	55.53	8.50	

Maximum patients in Group A were from age group of 61-70 years(46.7%) where as maximum patients in Group B were from age group of 51-60 years(40%).The mean age in Group A was 60.10 years ± 8.14, whereas mean age of Group B was 55.23 years ± 8.50(60.10 years ± 8.14 v/s 55.23 years ± 8.50). Patients with HCC were elderly individuals.

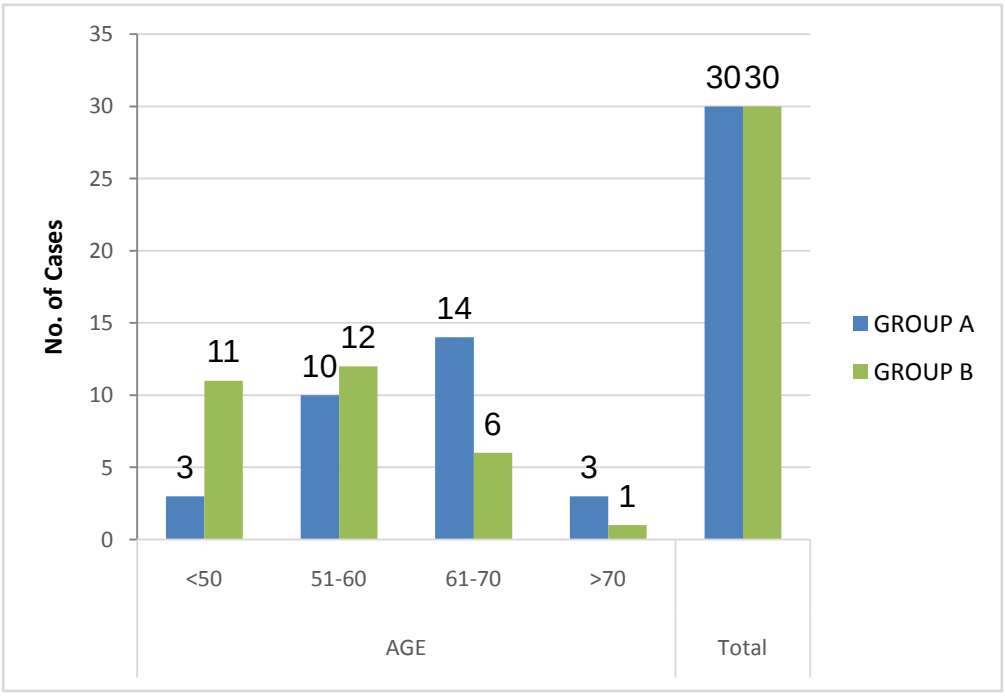

Figure 16: Age distribution of subjects in Group A and Group B

Table 5 : Sex distribution of subjects

SEX	No. of cases	Percentage
F	5	8.3%
M	55	91.7%
Total	60	100.0%

91.7 % of patients were Male, 8.3% were female

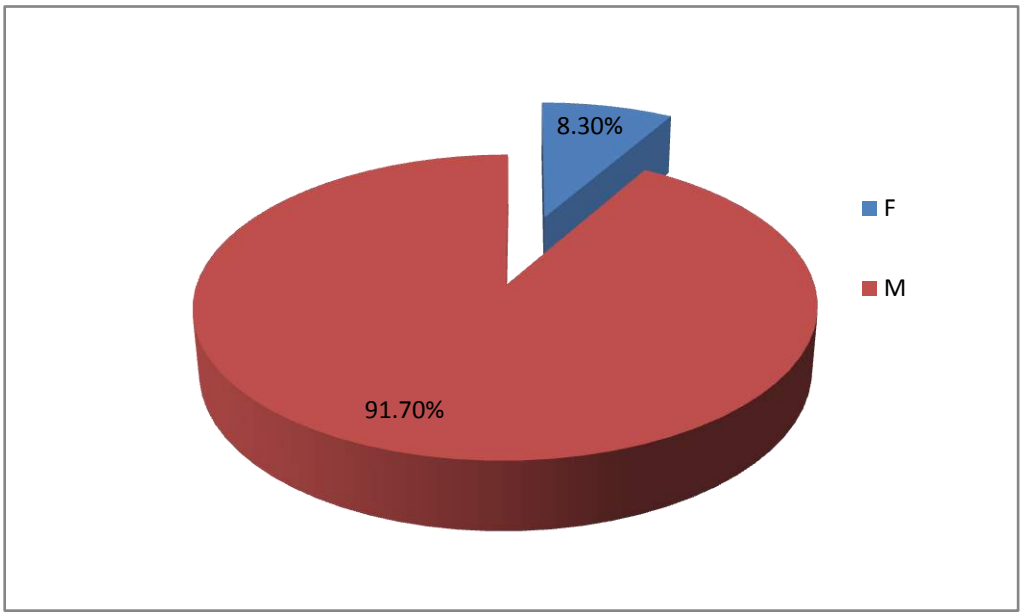

Figure 17: Sex distribution of subjects

Table 6 : Sex distribution of subjects in Group A and Group B

		GROUP A		GROUP B		Total
		No. of cases	%age	No. of cases	%age	
SEX	F	3	10.0%	2	6.7%	5
	M	27	90.0%	28	93.3%	55
	Total	30	100%	30	100%	60

In Group A 90.0 % of patients were Male, 10.0% were female

In Group B 93.3 % of patients were Male, 6.7% were female

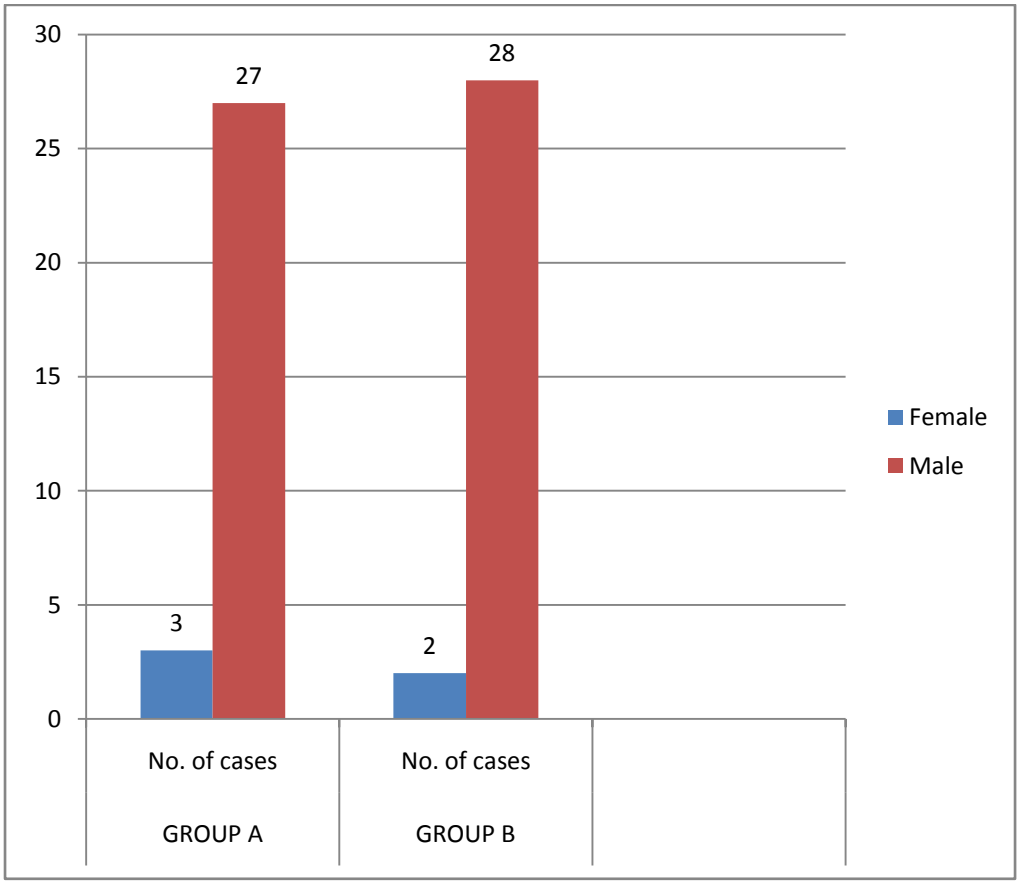

FIGURE 18: Sex distribution of subjects in Group A and Group B

Table 7: Etiology of Chronic Liver Disease

ETIOLOGY	No. of cases	Percentage
Hepatitis B	4	6.7%
Hepatitis C	21	35.0%
Alcohol	22	36.7%
Non Alcoholic Steatohepatitis	12	20.0%
Hepatitis B and Hepatitis C	1	1.7%
Total	60	100.0%

36.66% of patients had alcohol as etiology, 35% of patients had HCV as etiology, 6.66% of patients had HBV as etiology, 20% of patients had NASH as etiology and 1.66% had HCV and HBV as etiology.

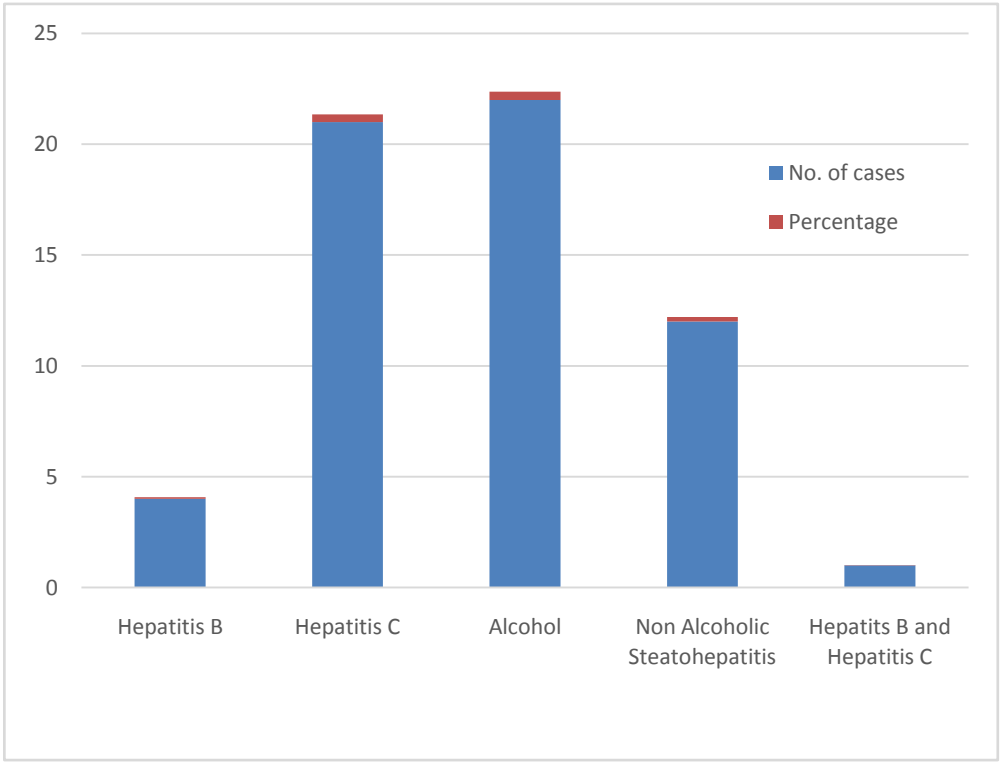

Figure 19: Etiology of Chronic Liver Disease

Table 8 : Etiology of CLD in Group A and Group B

	GROUP A		GROUP B	
	No. of cases	%age	No. of cases	%age
HEPATITIS B	2	6.7%	2	6.7%
HEPATITIS C	15	50.0%	6	20.0%
ALCOHOL	10	33.4%	12	40.0%
NASH	2	6.7%	10	33.3%
HBV and HCV	1	3.33%	-	-
TOTAL	30	100%	30	100%

In Group A 33.4% of patients had alcohol as etiology, 50.0% of patients had HCV as etiology, 6.7% of patients had HBV as etiology, 6.7% of patients had NASH as etiology and 3.33% had coexisting HCV and HBV as etiology.

In Group B 40.0% of patients had alcohol as etiology, 20.0% of patients had HCV as etiology, 6.7% of patients had HBV as etiology and 33.33% of patients had NASH as etiology .

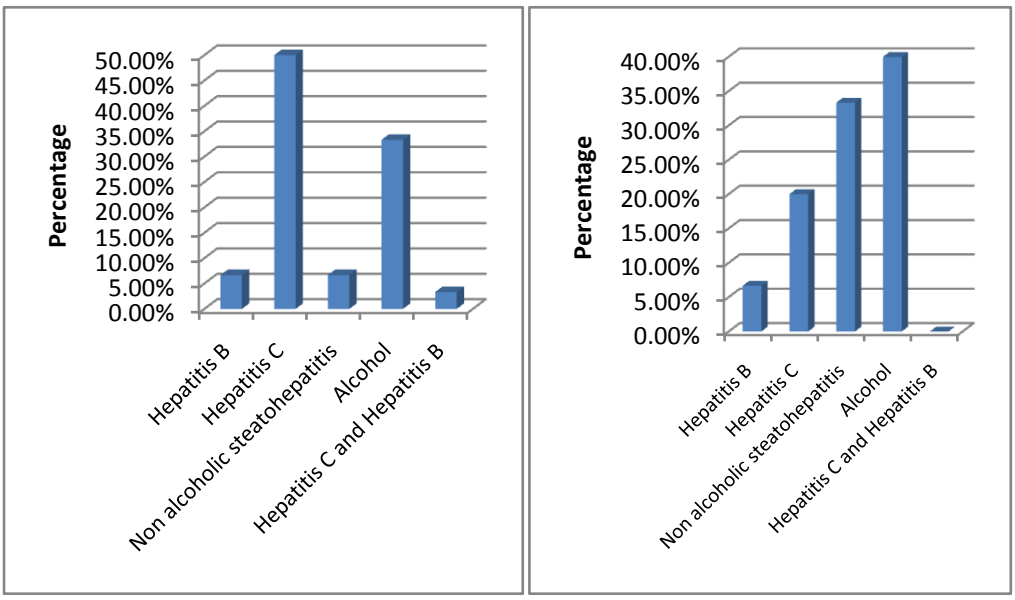

Figure 20 : Etiology of CLD in Group A and Group B

Table 9: Liver compensations status of patients with Cirrhosis in Group A and Group B

		GROUP A		GROUP B	
		No. of cases	%age	No. of cases	%age
LIVER DISEASE COMPENSATED	Absent	11	36.7%	0	0.0%
	Present	19	63.3%	30	100.0%
ASCITES (DECOMPENSATED)	Absent	24	80.0%	30	100.0%
	Present	6	20.0%	0	0.0%
JAUNDICE DECOMPENSATED	Absent	22	73.3%	30	100.0%
	Present	8	26.7%	0	0.0%
VARICEAL BLEED DECOMPENSATED	Absent	28	93.3%	30	100.0%
	Present	2	6.7%	0	0.0%
HEPATIC ENCEPHALOPATHY DECOMPENSATED	Absent	28	93.3%	30	100.0%
	Present	2	6.7%	0	0.0%
COAGULATION DEFECT DECOMPENSATED	NO	30	100.0%	30	100.0%

In our study Group B had compensated liver disease, whereas in Group A had 6 patients (20%) with ascites, 8 patients (26.7%) had jaundice, 2 patients(6.7%) had variceal bleed and 2 patients(6.7%) had hepatic encephalopathy.

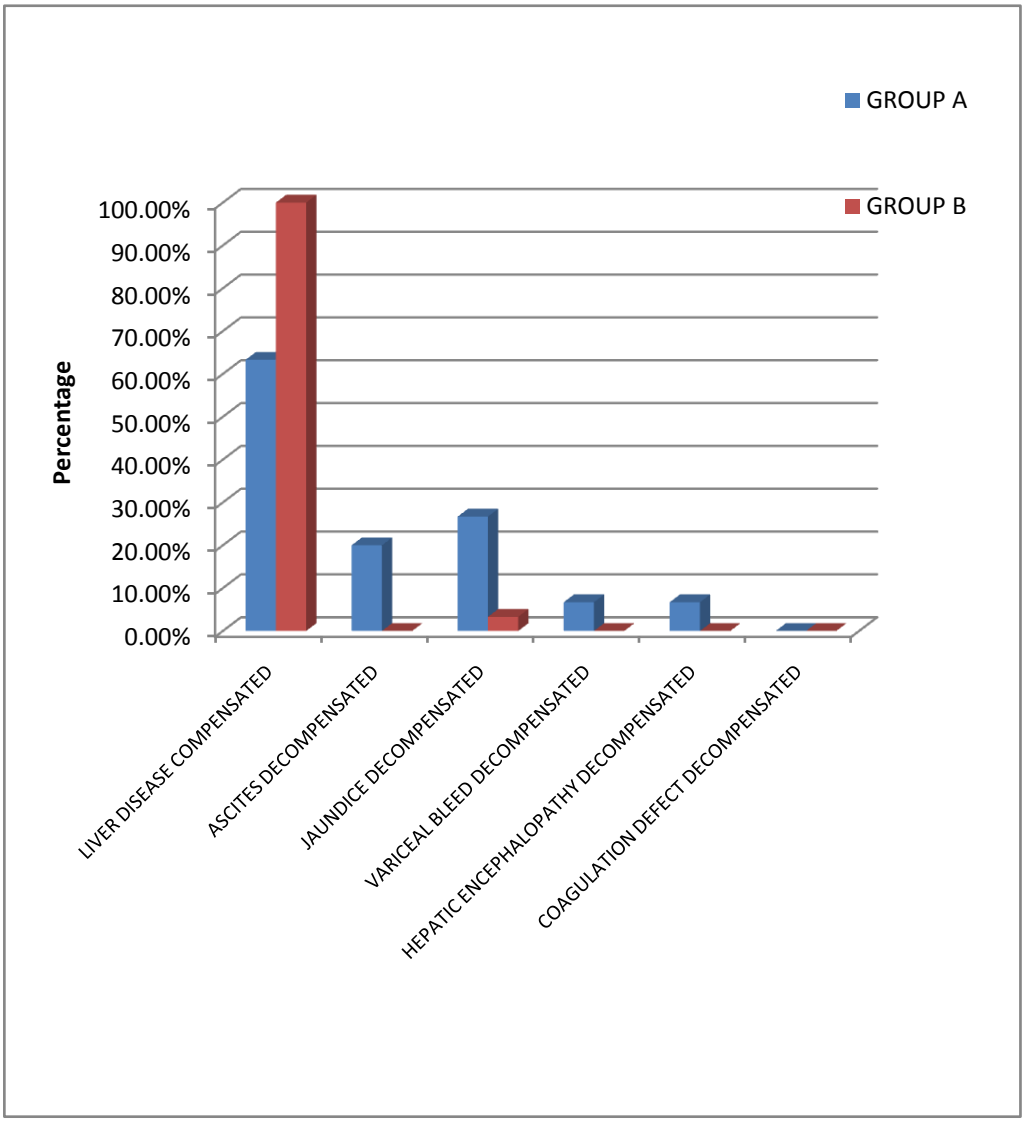

Figure 21: Liver compensations status of patients with Cirrhosis in Group A and Group B

Table 10 : Triphasic CT scan findings

		GROUP A		GROUP B	
		GROUP A	GROUP A	GROUP B	GROUP B
Space occupying lesion	Absent	0	0.00%	28	93.34%
	Present	30	100.00%	2	6.64%
Portal vein thrombosis	Absent	19	63.30%	29	96.70%
	Present	11	36.70%	1	3.30%

In our study 31 patients (51.7%) had space occupying lesion as evident Triphasic CT out of which 30 had malignant lesions LIRADS V and 1 patient had Benign lesion.

12 patients (20.0%) in our study had portal vein thrombosis as evident by CT scan. Out of which 11(36.7%) were having HCC and 1(3.3%) was having cirrhosis with HCC.

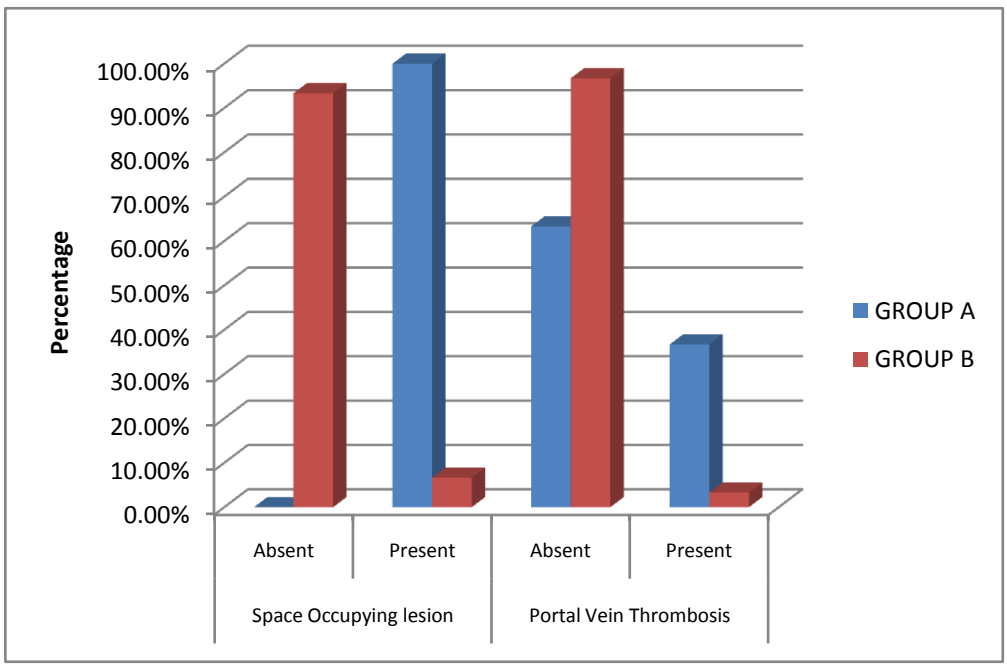

Figure 22 : Triphasic CT scan findings

Table 11 : Baseline characteristics of patients in Group A and Group B

	GROUP A		GROUP B		p-value
	Mean	SD	Mean	SD	
BMI	25.89	2.19	26.68	2.88	0.241
PLATELET	147435.47	97141.65	130933.33	56836.69	0.425
BILIRUBIN(T)	1.34	0.74	0.99	0.49	0.034
BILIRUBIN(D)	0.69	0.50	0.41	0.27	0.009
SGOT	89.47	80.22	68.90	48.55	0.235
SGPT	56.45	49.73	62.40	64.15	0.690
ALP	163.13	97.31	112.43	90.84	0.041
GGT	100.40	67.18	132.50	160.03	0.315
ALBUMIN	3.18	0.61	3.16	0.67	0.887
AFP	2257.35	6378.69	7.28	10.80	0.058

In our study we took cases and controls with similar characteristics. The mean BMIin Group A was 25.89± 2.19 whereas in Group B the mean BMI was 26.68±2.88.

Patients in Group A more platelet count 147.435 x 10^3± 97.141 x 10^3as compared to Group B patients where mean platelet count was 130.933 x 10^3± 56.836 x 10^3.

Patients with HCC has mean serum bilirubin of 1.34 ±0.74 mg/dl where as those without HCC had 0.99 ± 0.49 mg/dl

Both the groups had SGOT and SGPT below 5 times of the upper limit.

As expected the serum AFP levels were more in those with HCC, the mean serum AFP level in Group A was 2257.35 ± 6378.69 and in Group B it was 7.28 ± 10.80.

Table 12: Relationship of LSM and CAP with disease in Group A and Group B(median value)

	GROUP A		GROUP B		p-value
	Median	IQR	Median	IQR	
FIBROSCAN CONTROLLED ATTENUATION PARAMETER	259.00	233-286	261.50	206-293	0.477
FIBROSCAN LIVER STIFFNESS	58.00	46-70	24.50	18-37	0.000

In our study the median Controlled attenuation parameter value of Group A patients was 259.00 with IQR of 233-286 and 261.50 with IQR of 206-293 in Group B patients.

The median Liver stiffness measurement of Group A patients was 58.00 with IQR of 46-70 and 24.50 with IQR of 18-37 in Group B patients.

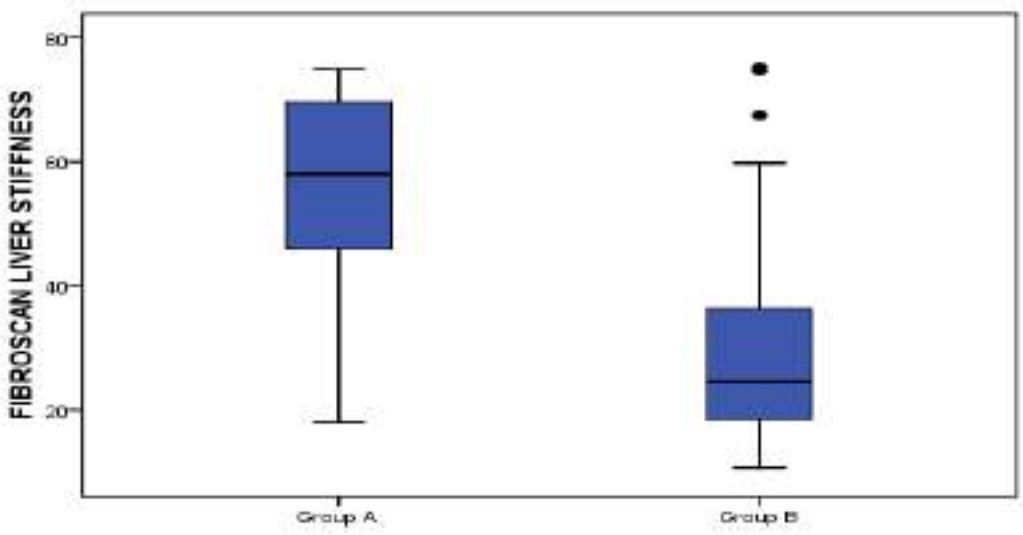

Figure 23: Relationship of LSM and CAP with disease in Group A and Group B(median value)

Table 13: Relationship of LSM and CAP with disease in Group A and Group B (mean value)

	GROUP A		GROUP B		p-value
	Mean	SD	Mean	SD	
FIBROSCAN CONTROLLED ATTENUATION PARAMETER	257.33	44.23	247.73	58.70	0.477
FIBROSCAN LIVER STIFFNESS	55.45	16.93	30.99	19.96	0.000

In our study the mean Controlled attenuation parameter value of Group A patients was 257.33 +/- 44.23 and 247.73 +/- 58.79 in Group B patients.

The mean Liver stiffness measurement of Group A patients was 55.45 +/- 16.93 and 30.99 +/- 19.96 in Group B patients.

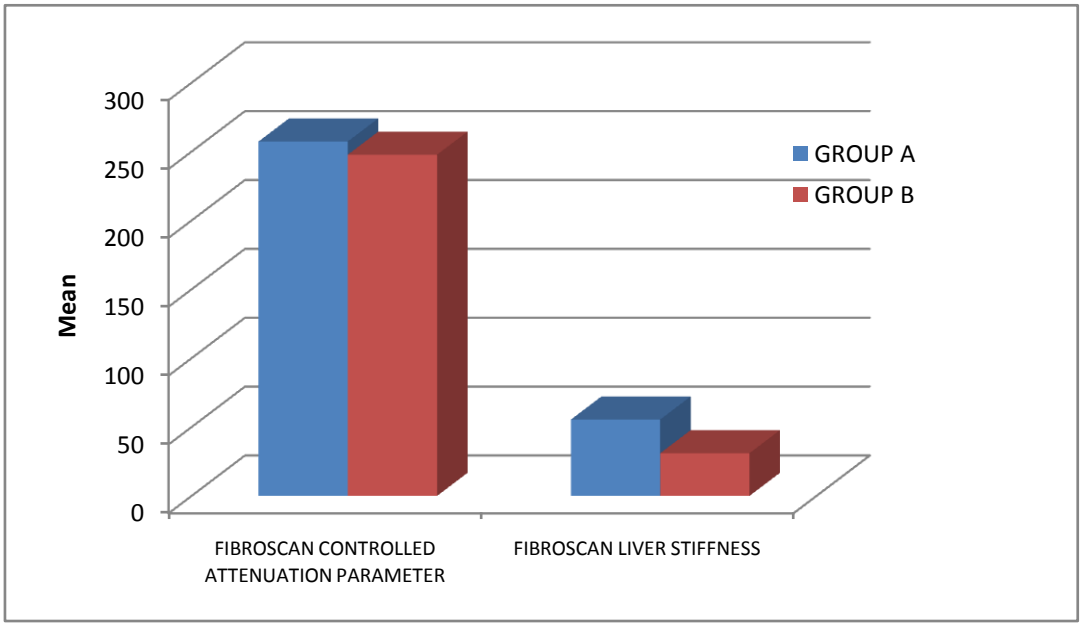

Table 24: Relationship of LSM and CAP with disease in Group A and Group B(mean value)

Table 14 : Stratum-specific likelihood ratio analysis of liver stiffness

		GROUP A		GROUP B		Total	
		No. of cases	%age	No. of cases	%age		SSLR(95% CI)
LSM	< 30	4	13.3%	20	66.7%	24	0.2 (0.08-0.52)
	30-50	5	16.7%	5	16.7%	10	1 (0.32-3.10)
	> 50	21	70.0%	5	16.7%	26	4.2 (1.82-9.67)
Total		30	100.0%	30	100.0%	60	

The likelihood ratio increased as we moved up the stratum. The likelihood ratio for group < 30 is 0.2, Likelihood ratio for group 30-50 is 1 and group>50 kPa is 4.2. As we increased above the stratum the likelihood ratio for HCC increased.

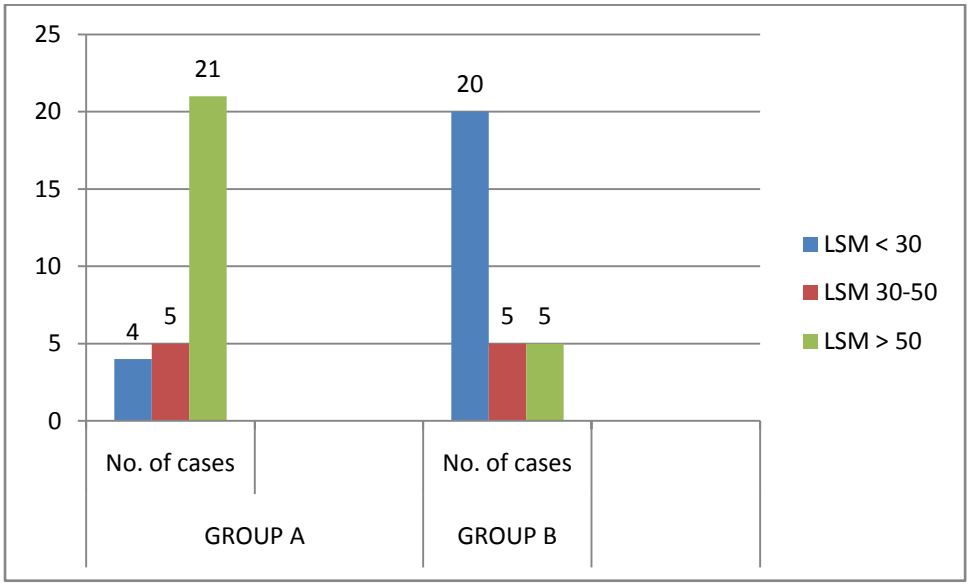

Figure 25:Stratum-specific likelihood ratio analysis of liver stiffness

Table 15: Stratum-specific likelihood ratio analysis of liver stiffness for HCV

		GROUP A		GROUP B		Total	
		No. of cases	%age	No. of cases	%age		SSLR(95% CI)
LSM	< 30	2	13.3%	5	100%	7	0.15(0.04-0.55)
	30-50	1	6.67%	0	0%	1	-
	> 50	12	80.0%	1	0%	13	4.8(0.79-29)
Total		15	100.0%	6	100.0%	21	

The likelihood ratio for HCC in patients with cirrhosis due to HCV increased as we moved up the stratum. The likelihood ratio for group < 30 is 0.15, Likelihood ratio for group 30-50 is and group >50 kPa is 4.8. As we increased above the stratum the likelihood ratio for HCC increased.

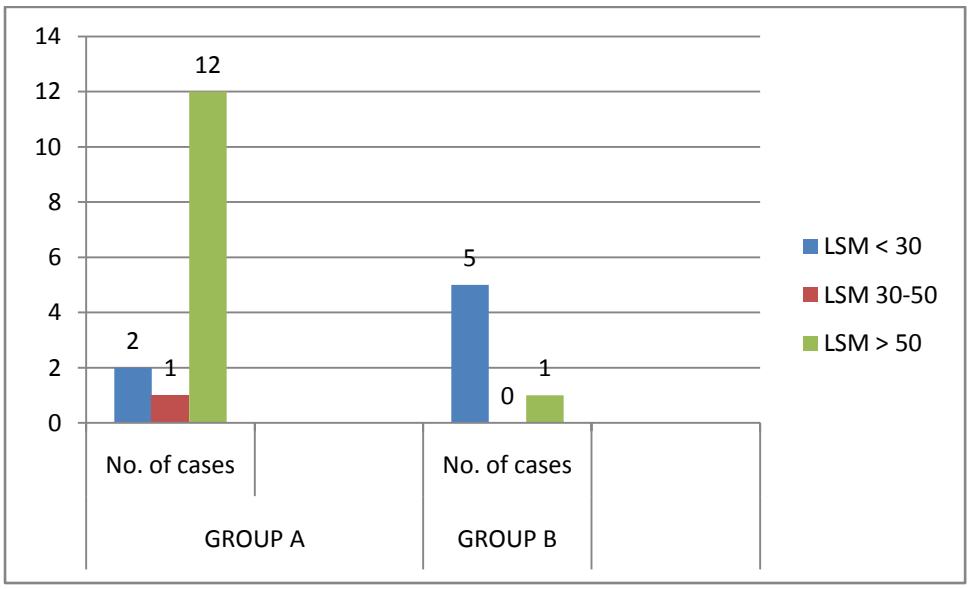

Figure 26: Stratum-specific likelihood ratio analysis of liver stiffness for HCV

Table 16: Stratum-specific likelihood ratio analysis of liver stiffness for Alcohol

		GROUP A		GROUP B		Total	
		No. of cases	%age	No. of cases	%age		SSLR(95% CI)
LSM	< 30	2	20.0%	7	58.33%	9	0.34(0.09-1.29)
	30-50	2	20.0%	3	36.0%	5	0.8(0.16-3.88)
	> 50	6	60.0%	2	16.67%	8	3.6(0.92-14.06)
Total		15	100.0%	12	100.0%	22	

The likelihood ratio for HCC in patients with cirrhosis due to alcohol increased as we moved up the stratum. The likelihood ratio for group < 30 is 0.34, Likelihood ratio for group 30-50 is 0.8 and group >50 kPa is 3.6. As we increased above the stratum the likelihood ratio for HCC increased.

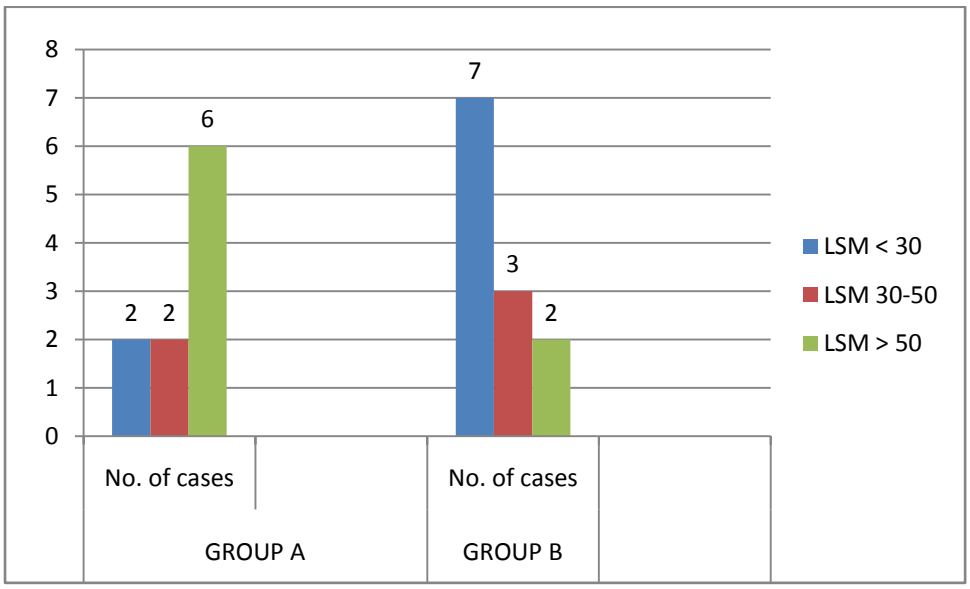

Figure 27: Stratum-specific likelihood ratio analysis of liver stiffness for Alcohol

Table 17:Univariate analysis of Bio clinical features associated with the risk of HCC

Characteristics	P-value
AGE	0.038
SEX	0.640
HEPATITIS C	0.033
ALCOHOL	0.032
PLATELET COUNT	0.425
DIABETES MELLITUS	0.015
BILIRUBIN(T)	0.034
ALBUMIN	0.887
AFP	0.058
LSM	<0.001

In a univariate analysis age, LSM, Etiology of cirrhosis (hepatitis C and alcohol),diabetes mellitus, total bilirubin were risk factors associated with HCC, whereas sex, platelet count, albumin and AFP were not associated as risk factors for HCC.

Table 18: Multivariate analysis of Bio clinical features associated with the risk of HCC

	P-VALUE	Exp(B)	95% C.I.for EXP(B)	
			Lower	Upper
AGE	0.010	1.168	1.038	1.313
PLATELET COUNT	0.668	1.000	1.000	1.000
BILIRUBIN(T)	0.231	2.344	0.581	9.457
ALBUMIN	0.539	0.681	0.200	2.315
AFP	0.268	1.000	1.000	1.000
LSM	0.011	1.052	1.012	1.094
HEPATITIS C	0.017	9.001	1.480	54.759
ALCOHOL	0.030	8.012	1.229	52.221

In a multivariate analysis age, LSM, Etiology of cirrhosis (hepatitis C and alcohol) were independent risk factors associated with HCC, whereas platelet count, bilirubin, albumin and AFP were not associated as risk factor for HCC.

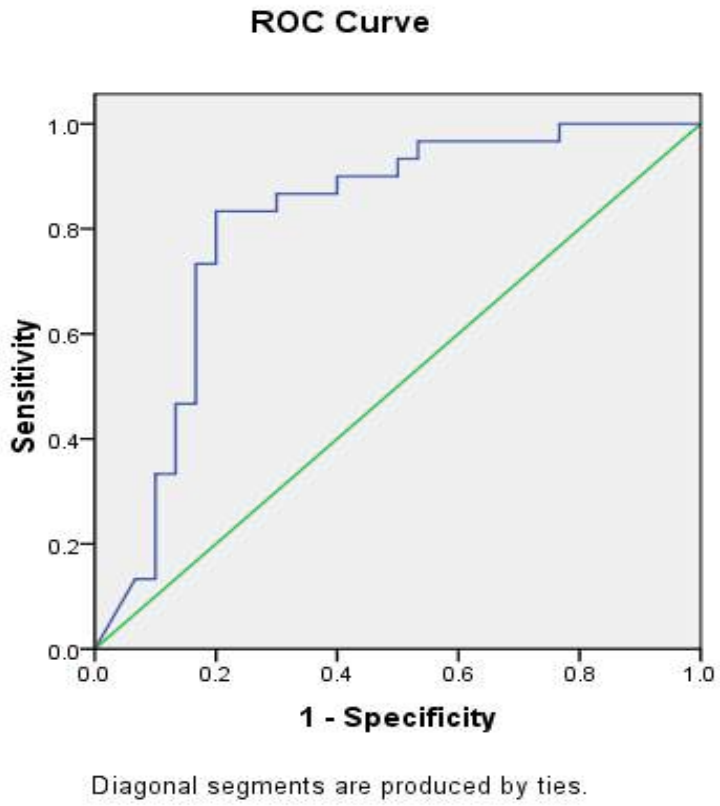

Figure 28: ROC Curve for Liver stiffness Measurement

Area Under the Curve

Test Result Variable(s):FIBROSCAN LIVER STIFFNESS

Area	Std. Error[a]	p-value	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
0.810	0.060	0.000	0.693	0.927

In the above ROC curve, AUROC is 0.810 which is near to 1 so increasing value of liver stiffness measurement is good predictor for HCC. At a cut-off value of LSM 39.35 the risk of HCC is highest.

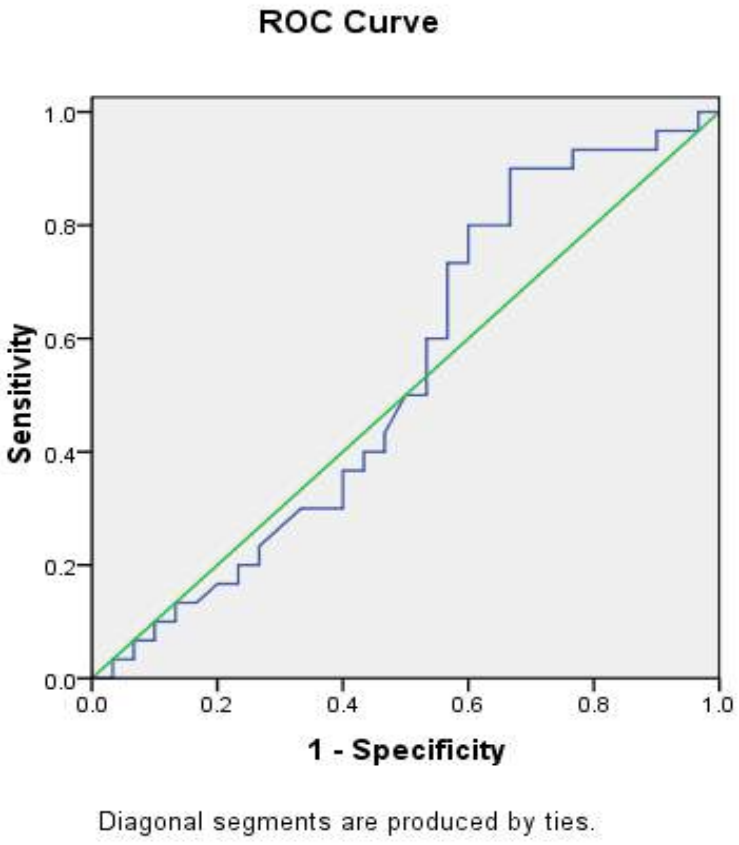

Figure 29: ROC for Controlled Attenuation Parameter

Area Under the Curve

Test Result Variable(s):FIBROSCAN CONTROLLED ATTENUATION PARAMETER

Area	Std. Error[a]	p-value	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
0.534	0.076	0.652	0.384	0.684

In the above ROC curve, AUROC is 0.534, so in our study the CAP is not a good predictor of HCC.

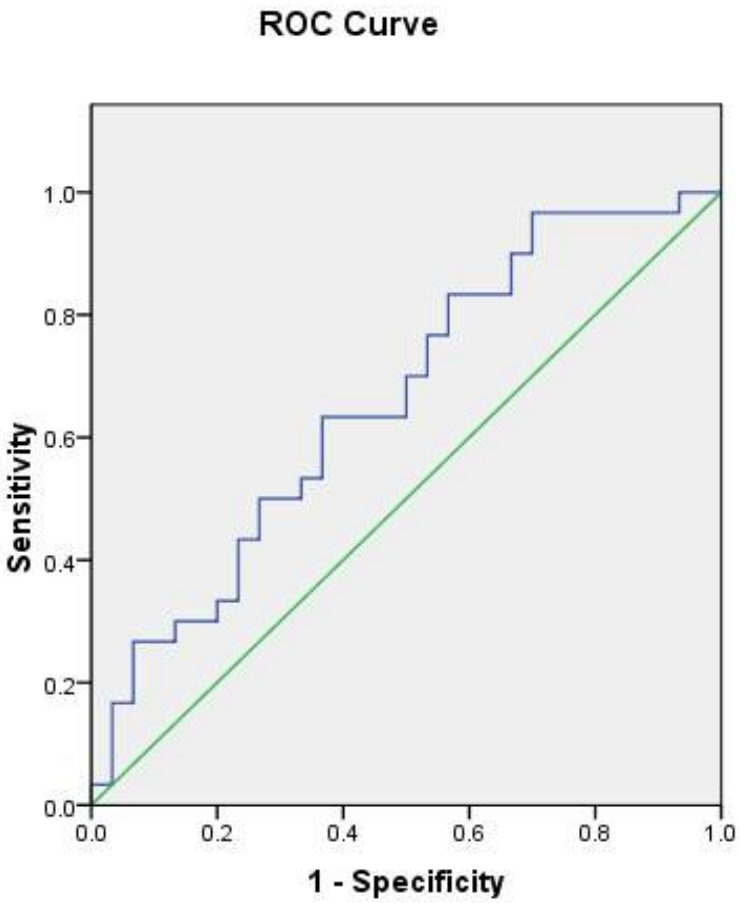

Figure 30: ROC for AFP

Area Under the Curve

Test Result Variable(s):AFP

Area	Std. Error[a]	p-value	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
0.660	0.070	0.033	0.522	0.798

In the above ROC curve, AUROC is 0.660, so in our study AFP is not a good predictor of HCC.

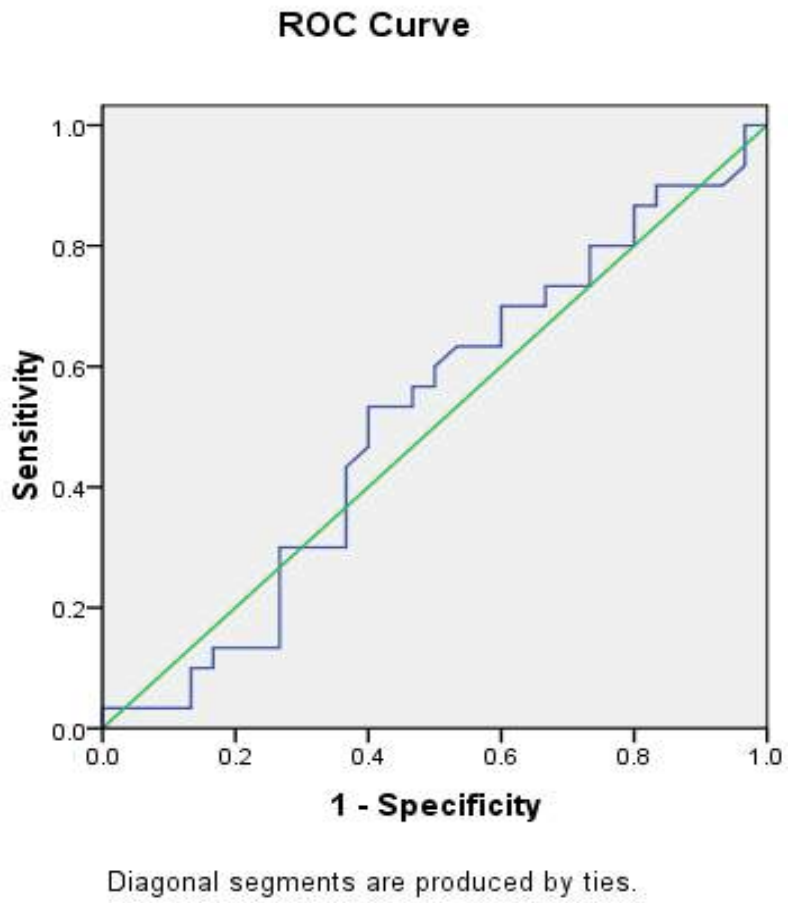

Figure 31: ROC for ALBUMIN

Area Under the Curve

Test Result Variable(s): ALBUMIN

Area	Std. Error[a]	p-value	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
0.515	0.076	0.842	0.366	0.664

In the above ROC curve, AUROC is 0.515, so in our study the Albumin is not a good predictor of HCC.

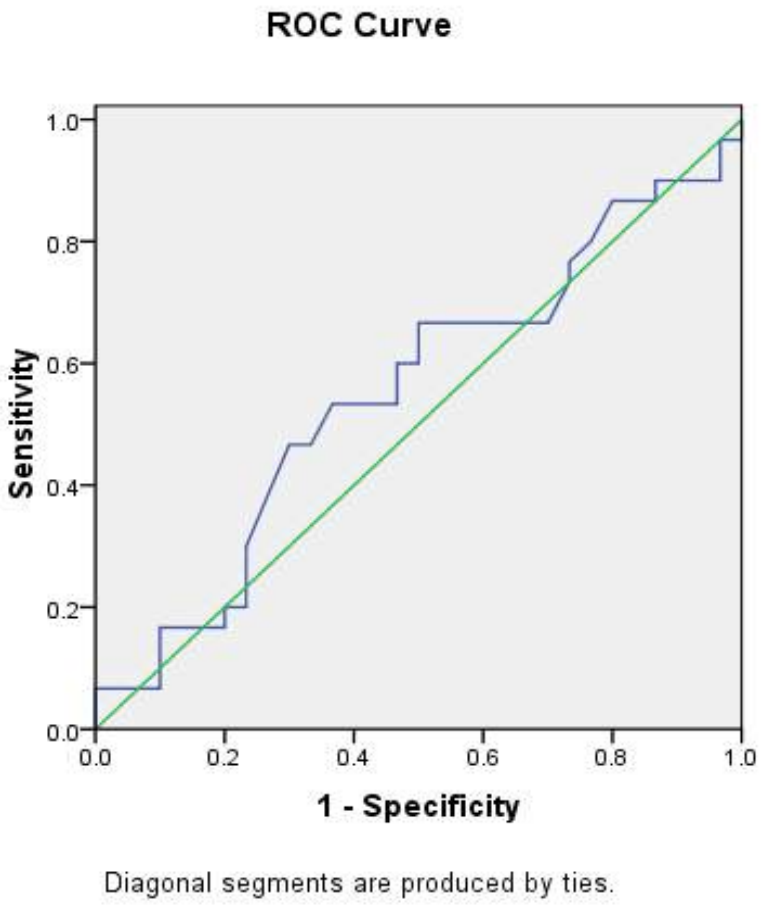

Figure 32: ROC for PLATELET COUNT

Area Under the Curve

Test Result Variable(s): ALBUMIN

Area	Std. Error[a]	p-value	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
0.552	0.075	0.492	0.404	0.699

In the above ROC curve, AUROC is 0.552, so in our study the platelet count is not a good predictor of HCC.

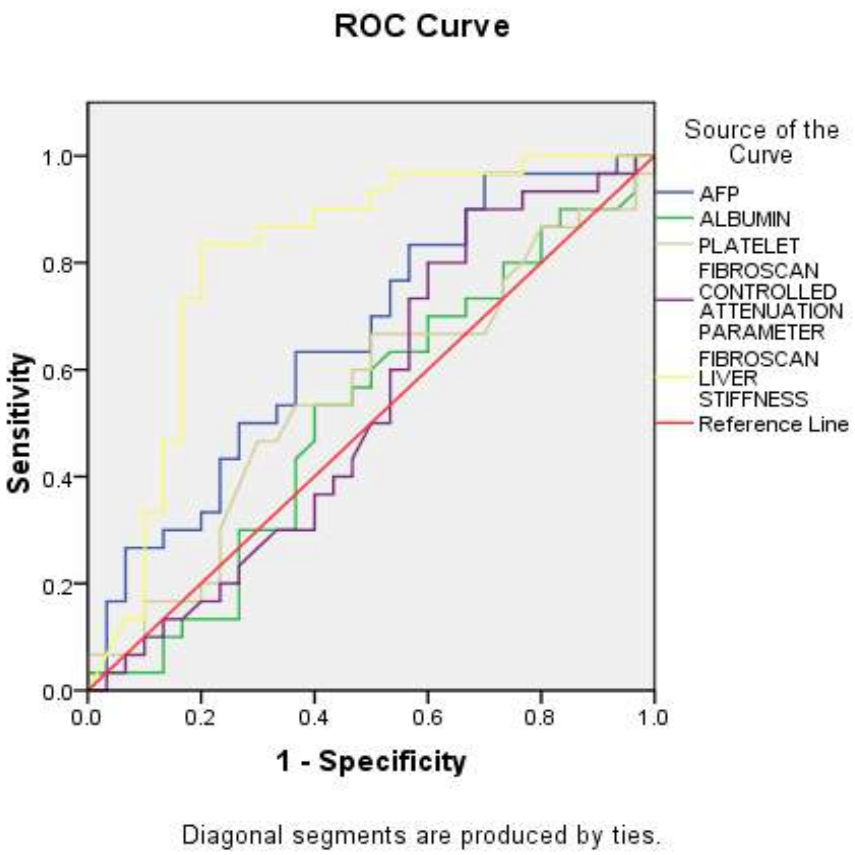

Figure 33: Comparison of AUROC of various bio clinical parameters

AUROC was highest for LSM (0.810), followed by AFP (0.660), platelet count (0.552), CAP(0.534) and albumin (0.515).

DISCUSSION

Liver fibrosis has been reported to be correlated with the risk of HCC and currently liver biopsy is considered as the best standard of care for the assessment of liver fibrosis. Liver histology and axial imaging are useful tools for diagnosing cirrhosis, but they cannot reliably divide cirrhosis into categories to reflect progressive disease. The liver biopsy carries many disadvantages starting from being an invasive procedure, cost, low sensitivity, sampling errors to serious complications such as death. Currently hepatocellular carcinoma is being diagnosed using ultrasonography, biochemical markers, CT scan, MRI and contrast enhanced USG. These are excellent in diagnosing HCC however radiation, cost and inter-observer bias are important drawbacks.

Recent studies conducted worldwide have shown that LSM can predict HCC. In our study, we used the same hypothesis and have tried for the non-invasive assessment of patients with chronic liver disease without hepatocellular carcinoma and patients with chronic liver disease with hepatocellular carcinoma irrespective of etiology.

The present study was conducted in tertiary hospital in North India. It was a cross-sectional study in design and involved 60 patients, out of which 30 patients had chronic liver disease with HCC and 30 patients had chronic liver disease without HCC. The statistical data hence obtained was compared with previous published literatures.

The mean age of patient with cirrhosis with HCC in our study was 60.1 years and in patients with cirrhosis without HCC the mean age was 55.53 years and in similar studies by Nahon P et al.[100] mean age in patients with cirrhosis with HCC was 65.7 years and in patients with cirrhosis without HCC was 57.1 years, In a similar cross-sectional study by Masuzaki et al.[93] on HCV related HCC naive patients the mean age was 67.5 years and in patients without cirrhosis it was 70.8 years. In another study conducted by Kuo et al.[101] on patients with

chronic hepatitis the mean age in patients with HCC was 61.8 years and in patients without HCC the mean age was 51 years.

Table 19: Mean age of patients in various studies

S.no	Study	Mean Age in patients with HCC	Mean Age in patients without HCC
1	Nahon P et al.[100]	57.1 ± 12.97	65.7± 10.48
2	Masuzaki et al.[93]	70.8 (64.7-75.3)	67.5 (61.3-72.4)
3	Kuo et al.[101]	51.0 ± 11.8	61.8 ± 11.8
4	Jung KS et al.[98]	55.5 ± 9.3	49.9 ± 9.9
5	Present study	60.1 ± 8.14	55.53 ± 8.50

Majority of our patients in our study were males in both groups cirrhosis with HCC (27/30)-90% and cirrhosis without HCC(28/30)-93.3% and in similar studies by Nahon P et al.[100] male sex patients with cirrhosis with HCC was 72.7% and in patients with cirrhosis without HCC was 63.3%. In another study conducted by Kuo et al.[101] male were more as compared to female in both groups that is 61.7% in patients with HCC and 84% in patients without HCC. It has been seen throughout the world that males have higher incidence rate as compared to females.[24]

The number patients with HCV as etiology of cirrhosis were 15/30 which constituted 50% of the total patients in those with HCC, alcohol related cirrhosis with HCC was 10/30 (33.4%), HBV related cirrhosis with HCC was 2/30(6.7%), NASH related HCC was 2/30(6.7%) and coexistent HCV and HBV with HCC was 1/30(3.3%). In study by Nahon P et al.[100] HCV as cause of HCC were 65.1% and alcohol as cause of HCC was 34.9%. In another study of mixed etiology by Kuo et al.[101] HCV as cause of HCC were 35%, HBV as cause of HCC was 44% and around 8.5% were of coexisting HBV and HCV .

The number patients with HCV as etiology of cirrhosis were 6/30(50%) in those without HCC, alcohol related cirrhosis without HCC was 12/30

(40.0%), HBV related cirrhosis without HCC was 2/30(6.7%) and NASH without HCC was 10/30(33.3%). In study by Nahon P et al.[100] HCV as cause of cirrhosis without HCC were 65.3% and alcohol as cause of cirrhosis without HCC were 34.7%. In another study of mixed etiology by Kuo et al.[101] HCV as cause of cirrhosis without HCC were 64.7% ,HBV as cause of cirrhosis without HCC were 26.4% and around 5.8% were of coexisting HBV and HCV cirrhosis without HCC.

Performing fibroscan in ascites is difficult, in our study the Group B patients were having compensated status where as Group A patients the 6 patients had ascites, most of the patients had minimal ascites which was not tapable or in case if the ascites was present we did a therapeutic ascitic tap and then performed the fibroscan, it has also been observed in a study by kohlhaas et al.[126] that liver stiffness values are not significantly altered in ascites until there is congestion present in liver.

Another contraindication to fibroscan is Jaundice, in our present study about 9 patients had raised serum bilirubin which was not due to extrahepatic cholestasis rather due to decompensated liver status, we performed fibroscan in all such patients when the serum bilirubin level was below 2.5 mg/dl. In present study the mean serum bilirubin in patients with HCC was 1.34 ± 0.74 and in patients without HCC 0.99 ± 0.49. In a similar study by Kuo et al.[101] the mean serum bilirubin in patients with HCC was 1.63 ± 4.39 and in patients without HCC it was 1.02 ± 0.88.

We performed Triphasic CT in all patients in which 32 patients had space occupying lesion whereas 28 patients had no space occupying lesion, out of the 32 patients with space occupying lesion 30 had LIRADS V lesion and only 2patients had benign lesion.

It have been seen in many cohort studies that the stiffer the liver the more is the risk of HCC. In a study conducted by Yoshida et al.[127] on chronic hepatitis C patients which was a cohort of 2800 patients found degree of liver fibrosis, age and male sex to be risk factors for HCC development, among which liver fibrosis was the strongest risk factor.

With fibroscan, stiffness of liver can be expressed as a continuous variable by LSM. This has an advantage over liver biopsy. Higher the values of LSM, more is the risk of HCC.

In our study, patients with HCC in the HCV, HBV, alcohol and NASH groups had higher LSM values than patients without HCC.

The increased LSM had a strong association with the presence of HCC along with other risk factors in univariate analysis such as advanced age and other biological factors. This is in concordance to study by Nahon P et al.[100] where increased LSM was a strong feature along with age as a predictor for HCC.

LSM remained increased in multivariate analysis as an independent risk factor. In our study Age and LSM were independently correlated with the presence of HCC. In a similar study Nahon P et al.[100] age and LSM were independently associated as a risk factor for HCC. In another study by Masuzaki et al.[93] on HCV patients, authors did a multivariate analysis and found liver stiffness, age, male and AFP as risk factors associated with HCC. In a study conducted by Jung KS et al.[98] on 1,130 chronic hepatitis B patients found similar independent risk association and found that older age, male sex, heavy alcohol consumption, HBeAg positivity as risk factors for HCC development. In contrast, in our study AFP levels did not contribute as a risk factor HCC development. As per a study by Carr B.I. et al.[128] AFP levels are poor screening tools for detection of HCC. In our study we didn't find high ALT as risk factors for HCC development, because our study had an exclusion criteria of high risk patients with elevated ALT. Exclusion of high ALT patients may result in selection bias in our study, but it was necessary to increase the reliability of LSM.[118,120]

In our study we performed fibroscan in all patients with HCC irrespective of aetiology. We found that LSM values were higher in patients with HCV as compared to patients with alcohol as aetiology. The median LSM values were higher in HCV. This is contrast to study by Nahon P et al.[100] where patients with alcohol as etiology of cirrhosis with HCC had higher LSM values. In our study we did a multivariate analysis as per etiology of the cirrhosis with LSM and found that the

HCV as an independent risk factor contributed more as compared to alcohol, where as the author Nahon P et al.[100] didn't do a multivariate analysis of HCV and alcohol.

In our study we divided the study population into 3 groups using the stratified LSM, the proportion of patients increased significantly in groups with higher LSM. Since our study is a cross-sectional study, where risk ratios cannot be calculated, it has been seen that likelihood ratios are known to approximate risk ratios. The likelihood ratio for group < 30 is 0.2(95% CI 0.08-0.52), Likelihood ratio for group 30-50 is 1(95% CI 0.32-3.10) and group >50 kPa is 4.2(95% CI 1.82-9.67). As we increased above the stratum the likelihood ratio for HCC increased. In a similar study by Kuo et al.[101] the likelihood ratio for patients with chronic hepatitis with HCC increased with the increase in strata.

We compared the likelihood ratio for development of HCC as per different etiologies. We found that results were same, that is as we move up the stratum the risk of HCC increases. The likelihood ratio for HCC in patients with cirrhosis due to HCV increased as we moved up the stratum. The likelihood ratio for group < 30 is 0.15(95% CI 0.04-0.55), and increased further in the stratum with group >50 kPa being 4.8(95% CI 0.79-29). As we increased above the stratum the likelihood ratio for HCC increased. In a similar study by Masuzaki et al.[93] on patients with HCV related cirrhosis the likelihood increased as they moved up the stratum. In a similar cohort study by Adler et al.[3] on 432 patient with already established cirrhosis with an LS value >20 kPa found similar conclusion that as we move above the strata there is an increase in risk of HCC.

The likelihood ratio for HCC in patients with cirrhosis due to alcohol increased as we moved up the stratum. The likelihood ratio for group < 30 is 0.34(95% CI 0.09-1.29), Likelihood ratio for group 30-50 is 0.8(95% CI 0.16-3.88) and group >50 kPa is 3.6(95% CI 0.92-14.06). As we increased above the stratum the likelihood ratio for HCC increased.

It was observed that for patients with HCV related cirrhosis with HCC the likelihood ratio increased more as compared to alcohol.

In the present study we could not stratify patients with HBV and NASH related HCC due to limited sample population.

In our study AUROC when compared for LSM and different biological factors, it was seen that AUROC was highest for LSM (0.810), followed by AFP (0.660), platelet count (0.552) and albumin (0.515). In a similar study conducted by Masuzaki et al.[93] the AUROC was highest for liver stiffness(0.805), then followed by AFP (0.741), albumin (0.741), platelet count (0.654). In a similar study by Kuo et al.[101] AUROC for HCC presence was highest for LSM (0.736), followed by AFP (0.733) and platelet count (0.594).

Table:20 AUROC of bio clinical parameters of patients in various studies

S.no	AUROC	Masuzaki et al.[93]	Kuo et al.[101]	Present study
1	LSM	0.805	0.736	0.810
2	AFP	0.741	0.733	0.660
3	Platelet Count	0.654	0.594	0.552
4	Albumin	0.741	-	0.515

Analyzing AUROC, it was observed that LSM had highest AUROC, which is an indirect measurement for assessing risk of HCC whereas AFP is a biomarker specific to HCC. In many studies it has been seen that AFP level may be normal in 35% to 45% patients suffering from HCC, and the sensitivity of this test falls further with the decrease in size of malignant lesion. [129,130] Also elevated levels of AFP can be seen in patients with cirrhosis or chronic hepatitis without HCC which probably due to inflammation and hepatocyte regeneration.

In our study we found a cut-off 39.35 kPa as useful with a sensitivity of 83% and a specificity of 80% in predicting the presence of HCC .In a similar study by Kuo et al.[101] on chronic hepatitis patients, they found a cut-off 24 kPa as useful with a specificity of more than 90% in predicting the presence of HCC. In a prospective study by J Foucher et al.[10] showed that transient elastography is an excellent efficient

technique for the diagnosis of cirrhosis and its severity. They found a cut-off 53.7 kPa for establishing HCC. The differences in research demographics and etiologies of recruited patients could explain the disparity in cut-offs between studies.

Finally in our study included 2 patients who had benign lesion as per contrast enhanced CT scan. One patient had multiple lesions in both lobes and had a LSM value of 25.3 kPa, and another patient had a benign lesion in right lobe of liver and had LSM of 75 kPa therefore, it would be matter of research that whether elastography can distinguish between benign lesions from malignant lesions.

LIMITATIONS

- Single centre study.
- As a cross-sectional study, we suffered from the common flaws. During our design, to make potential groups comparable, inclusion and exclusion criteria were defined, which caused a relatively small sample.
- Defining optimal threshold of LSM values for the risk of HCC in cross-sectional studies is not recommended, large prospective studies are still needed to assess the risk of HCC and other complications of cirrhosis according to LSM values in homogenous group of patients
- Our study results can only be applied to a subpopulation of patients showing limited ALT levels (< 10 times of upper limit of normal). However, when ALT levels become normal the reliability of LSM increases.
- Our study cannot estimate the future changes in the risk of HCC

SUMMARY AND CONCLUSION

- Patients with HCC have higher LSM values as compared to patients without HCC
- Transient elastography has the advantage of being non-invasive
- Liver histology and radiological imaging are useful in diagnosis of cirrhosis but these modalities cannot divide cirrhosis into different categories to reflect disease progression. As LSM is continuous variable it can be stratified and patients with high LSM values are at risk of HCC development and should be surveyed regularly with imaging studies.
- To achieve cost-effective outcomes for patients with chronic hepatitis or cirrhosis, there may be different screening or monitoring programmes for hepatocellular carcinoma stratified by liver stiffness values.
- A cut-off value of 39.35 kPa useful with a sensitivity of 83% and a specificity of 80% for predicting the presence of HCC.

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					ETIOLOGY						PERSONAL HISTORY		COMORBITIES							EXAMINATION				
S.NO	MRD NO	NAME	AGE	SEX	HEPATITIS B	HEPATITIS C	NON-ALCOHOLIC FATTY LIVER DISEASE	NON ALCOHOLIC STEATO HEPATITIS	INBORN ERRORS OF METABOLISM	AUTOIMMUNE LIVER DISEASE	ALCOHOL	SMOKING	HYPERTENSION	TYPE 2 DIABETES MELLITUS	CORONARY ARTERY DISEASE	CHRONIC OBSTRUCTIVE AIRWAY DISEASE	OBESITY	SEIZURE	PREVIOUS SURGERY	HEIGHT	WEIGHT	BMI	BP	PR
1	301874	KK	59Y	F	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO	NO	NO	YES	NO	YES	165 CM	80.25 KGS	29.48KG/M2	100/60MMHG	96/MIN
2	934660	CS	60Y	M	NO	NO	NO	NO	NO	NO	YES	NO	YES	YES	YES	NO	YES	YES	YES	168 CM	84 KGS	28.3KG/M2	110/70MMHG	94/MIN
3	32137	JK	55Y	F	NO	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	170 CM	86.4 KGS	29.91KG/M2	120/80MMHG	80/MIN
4	930484	AK	65Y	M	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	172 CM	86 KGS	29.15KG/M2	120/80MMHG	86/MIN
5	937674	PS	47Y	M	NO	NO	NO	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO	NO	NO	176 CM	90 KGS	29.1KG/M2	110/70MMHG	80/MIN
6	948782	RS	66Y	M	NO	NO	NO	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO	NO	NO	184 CM	95 KGS	27KG/M2	110/80MMHG	82/MIN
7	246992	VK	38Y	M	NO	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	168 CM	70 KGS	24.82KG/M2	130/80MMHG	76/MIN
8	999410	SS	65Y	M	NO	YES	NO	YES	NO	NO	NO	NO	YES	NO	NO	NO	NO	NO	YES	165 CM	64 KGS	23.1KG/M2	130/80MMHG	91/MIN
9	1079099	SK	52Y	M	NO	NO	NO	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO	NO	NO	175 CM	90 KGS	29.9KG/M2	120/80MMHG	86/MIN
10	1112064	DS	50Y	M	NO	NO	NO	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO	NO	NO	173 CM	65 KGS	21KG/M2	130/80MMHG	72/MIN
11	1123737	MS	50Y	M	NO	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	171 CM	70 KGS	24KG/M2	110/70MMHG	86/MIN
12	1120411	MS	60Y	M	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	170 CM	87 KGS	28.5KG/M2	120/80MMHG	106/MIN
13	1124941	HS	54Y	M	NO	NO	NO	NO	NO	NO	YES	NO	NO	YES	NO	NO	NO	NO	NO	165 CM	67 KGS	23.8KG/M2	120/80MMHG	80/MIN
14	1127084	RS	76Y	M	NO	NO	NO	YES	NO	NO	NO	NO	NO	YES	NO	NO	NO	NO	NO	170 CM	70 KGS	23.5KG/M2	120/80MMHG	78/MIN
15	1104873	AA	63Y	M	NO	NO	NO	YES	NO	NO	NO	NO	YES	YES	NO	NO	NO	NO	NO	168 CM	68 KGS	24.2KG/M2	140/70MMHG	74/MIN
16	1122170	JS	47Y	M	NO	NO	NO	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO	NO	NO	168 CM	82.3 KGS	29.2KG/M2	130/80MMHG	80/MIN
17	1129575	RK	49Y	M	NO	NO	NO	YES	NO	NO	NO	NO	YES	YES	NO	NO	YES	NO	NO	165 CM	85 KGS	29KG/M2	120/80MMHG	80/MIN
18	1129556	GS	47Y	M	NO	YES	NO	NO	NO	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO	167 CM	56 KGS	20KG/M2	160/100MMHG	76/MIN
19	1156876	RS	57Y	M	NO	YES	NO	NO	NO	NO	NO	NO	NO	YES	NO	NO	NO	NO	NO	180 CM	75 KGS	22.4KG/M2	130/80MMHG	87/MIN

				LIVER DISEASE																					
					DECOMPENSATED																				
S.NO	MRD NO	RR	TEMP	COMPENSATED	ASCITES	JAUNDICE	VARICEAL BLEED	HEPATIC ENCEPHALOPATHY	COAGULATION DEFECT	1. TLC	2. DLC	3. HB	4. PLATELET	5. BILIRUBIN (T)	6. BILIRUBIN (D)	7. SGOT	8. SGPT	9. ALP	10. GGT	11. TOTAL PROTEIN	12. ALBUMIN	13. BLOOD UREA	14. SERUM CREATININE	15. SERUM SODIUM	16. SERIM POTASSIUM	17. SERUM CHLORIDE
1	301874	20/MIN	99.2 F	YES	NO	NO	NO	NO	NO	11000	67.8/17.6/12.8/1.3/0.5	11.1	273000	1.2	0.58	65	22	131	33	7.1	2.76	28	0.86	134	4.58	99
2	934660	20/MIN	98.7 F	YES	NO	NO	NO	NO	NO	21600	76.2/16.3/6/1.1/0.4	10.2	228000	1.12	1.83	62	22	168	124	5.8	1.87	181	3.79	136	4.92	103
3	32137	20/MIN	98.6 F	YES	NO	NO	NO	NO	NO	7700	60.5/22.4/10.9/5.5/0.7	10.6	150000	1.12	0.92	43	24	135	23	6.4	2.2	23	0.65	141	3.53	106
4	930484	20/MIN	98.6 F	YES	NO	NO	NO	NO	NO	4100	66.6/20.5/10.3/1.9/0.7	8.4	140000	0.66	0.16	23	22	70	66	4.9	2.39	115	2.31	139	3.58	111
5	937674	20/MIN	98.6F	YES	NO	NO	NO	NO	NO	7000	82.8/14/3/0.1/0.4	7.6	90000	0.5	0.26	70	78	88	36	6.6	3.89	18	0.76	130	4.77	130
6	948782	20/MIN	98.8F	YES	NO	NO	NO	NO	NO	12000	71.6/17/5/8/2.4/0.5	10.6	256000	0.37	0.21	22	19	68	69	5.7	3.51	13	0.86	131	4.64	101
7	246992	16/MIN	98.9F	YES	NO	NO	NO	NO	NO	5000	67.7/20.7/10.5/0.7/0.4	10.5	181000	1.27	0.4	198	240	257	184	8.6	3.18	16	0.59	129	4.26	97
8	999410	16/MIN	98.6F	YES	NO	NO	NO	NO	NO	4000	85.4/10.6/3,8/0.1	7.6	48000	0.6	0.19	94	44	133	77	5.9	2.54	129	4.16	134	4.27	103
9	1079099	20/MIN	98.4F	YES	NO	NO	NO	NO	NO	5400	54.8/31.9/10.5/2.2/0.6	14.4	134000	0.57	0.3	65	149	84	184	7.2	4.13	14	0.81	138	4.21	103
10	1112064	20/MIN	98F	YES	NO	NO	NO	NO	NO	7700	69/27/3/1/0	7.9	106000	1.4	0.7	38	25	72	20	7	2.8	30	2.8	134	3.4	96
11	1123737	16/MIN	98.6F	YES	NO	NO	NO	NO	NO	4200	58.8/26.4/9.8/4.3/0.7	10.4	136000	1.03	0.33	105	34	99	72	8.2	2.29	28	0.6	130	4.15	99
12	1120411	18/MIN	101F	YES	NO	NO	NO	NO	NO	5600	70.7/15/10.3/3.5/0.5	11.7	142000	1.01	0.46	40	20	103	93	6.1	2.84	24	1	133	3.89	102
13	1124941	12/MIN	98.6F	YES	NO	NO	NO	NO	NO	3500	51.3/35.3/9.2/3.5/0.7	11.8	196000	1.17	0.65	49	20	184	337	6	2.34	13	0.68	134	4.21	107
14	1127084	20/MIN	98.6F	YES	NO	NO	NO	NO	NO	5500	53.4/31.7/10.6/4.1/0.2	8.7	118000	0.42	0.1	22	13	87	151	9.1	3.09	110	5.02	134	4.13	106
15	1104873	20/MIN	98.6F	YES	NO	NO	NO	NO	NO	6600	84.1/7.8/6.8/1/0.3	7.5	114000	0.61	0.18	155	262	55	34	5.3	2.58	91	6.46	145	3.71	107
16	1122170	20/MIN	98.6F	YES	NO	NO	NO	NO	NO	7100	53.9/32.2/11.4/2.1/0.4	13.8	189000	0.45	0.19	26	20	64	36	8	4.14	32	1.12	141	4.48	105
17	1129575	16/MIN	97.6F	YES	NO	NO	NO	NO	NO	4900	57.5/25/13/8/3.1/0.6	8.5	120000	1.14	0.65	40	21	75	90	5.9	3.03	57	0.9	141	4.1	106
18	1129556	16/MIN	98.9F	YES	NO	NO	NO	NO	NO	6300	61.8/20.4/13.1/4.3/0.4	15.9	136000	0.51	0.12	67	70	78	97	7.4	3.59	44	0.8	141	3.64	107
19	1156876	20/MIN	98.6F	YES	NO	NO	NO	NO	NO	6100	73.3/16/6/8.8/11.1/0.2	8.6	60000	0.71	0.13	98	145	65	318	5.7	3.21	85	0.62	141	5.09	112

		LABORATORY																					
							23. ULTRASONOGRAPHY				24. UPPER GI ENDOSCOPY				25. CT SCAN				26. MRI(IF DONE)				27. FIBROSCAN	
											• PHG(+/-)													
S.NO	MRD NO	18. HBsAG(ELISA)	19. ANTI HBC TOTAL	20. ANTI HCV(ELISA)	21. HIV	22. AFP	• SOL(+nt)/(-nt)	• SIZE	• LOBE/SEGMENT	• PVT(+nt)/(-nt)	Mild	Severe	• VARICES(+/-)	• EVL(+/-)	• SOL(+nt)/(-nt)	• SIZE	• LOBE/SEGMENT	• PVT(+nt)/(-nt)	• SOL(+nt)/(-nt)	• SIZE	• LOBE/SEGMENT	• PVT(+nt)/(-nt)	• CONTROLLED ATTENUATION PARAMETER	• LIVER STIFFNESS
1	301874	0.39	1.38	0.04	0.21	2.48	NO	N/A	N/A	NO	NO	YES	YES	YES	NO	N/A	N/A	NO	N/D	N/D	N/D	N/D	297 DB/M	25.1 KPA
2	934660	0.66	1.32	0.08	0.3	1	NO	N/A	N/A	NO	NO	NO	NO	NO	NO	N/A	N/A	NO	N/D	N/D	N/D	N/D	152 DB/M	13.6 KPA
3	32137	0.8	1.2	74.88	0.37	9.36	NO	N/A	N/A	NO	NO	YES	YES	NO	NO	N/A	N/A	YES	N/D	N/D	N/D	N/D	195 DB/M	26.2 KPA
4	930484	0.52	1.45	0.07	0.26	1.2	NO	N/A	N/A	NO	NO	NO	NO	NO	NO	N/A	N/A	NO	N/D	N/D	N/D	N/D	277 DB/M	12.5 KPA
5	937674	0.6	1.62	0.08	0.29	2.75	NO	N/A	N/A	NO	NO	NO	NO	NO	NO	N/A	N/A	NO	N/D	N/D	N/D	N/D	262 DB/M	20.7 KPA
6	948782	1.84	2	0.06	0.25	2.24	NO	N/A	N/A	NO	NO	NO	NO	NO	NO	N/A	N/A	NO	N/D	N/D	N/D	N/D	221 DB/M	18.6 KPA
7	246992	0.15	1.26	97.12	0.06	2.41	NO	N/A	N/A	NO	YES	NO	YES	YES	NO	N/A	N/A	NO	N/D	N/D	N/D	N/D	197 DB/M	59.8 KPA
8	999410	0.48	1.16	0.08	0.12	0.77	NO	N/A	N/A	NO	YES	NO	NO	NO	NO	N/A	N/A	NO	N/D	N/D	N/D	N/D	193 DB/M	10.7 KPA
9	1079099	0.2	1.16	0.66	0.1	15.11	NO	N/A	N/A	NO	YES	NO	YES	NO	NO	N/A	N/A	NO	N/D	N/D	N/D	N/D	286 DB/M	34.7 KPA
10	1112064	0.45	1.24	0.06	0.32	2.46	NO	N/A	N/A	NO	NO	YES	YES	YES	NO	N/A	N/A	NO	N/D	N/D	N/D	N/D	208 DB/M	48 KPA
11	1123737	0.24	1.72	49.99	0.75	5.59	NO	N/A	N/A	NO	YES	NO	NO	NO	NO	N/A	N/A	NO	N/D	N/D	N/D	N/D	100 DB/M	23.9 KPA
12	1120411	0.35	0.01	0.06	0.35	6.66	NO	N/A	N/A	NO	YES	NO	NO	NO	NO	N/A	N/A	NO	N/D	N/D	N/D	N/D	238 DB/M	37.3 KPA
13	1124941	0.33	1.34	0.9	0.25	4.63	YES	N/M	DIFFUSE	NO	NODULAR PHG	NO	NO	NO	YES	MULTIPLE	RIGHT AND LEFT	NO	N/D	N/D	N/D	N/D	251 DB/M	25.3 KPA
14	1127084	0.24	1.25	0.06	0.23	5.19	NO	N/A	N/A	NO	YES	NO	NO	NO	NO	N/A	N/A	NO	N/D	N/D	N/D	N/D	313 DB/M	29.4 KPA
15	1104873	0.18	1.2	0.08	0.26	1.18	NO	N/A	N/A	NO	YES	NO	NO	NO	NO	N/A	N/A	NO	N/D	N/D	N/D	N/D	149 DB/M	27.2 KPA
16	1122170	0.36	1.08	0.15	0.26	6.22	NO	N/A	N/A	NO	NO	YES	YES	YES	NO	N/A	N/A	NO	N/D	N/D	N/D	N/D	318 DB/M	75 KPA
17	1129575	0.35	2	0.07	0.24	3.28	NO	N/A	N/A	NO	YES	NO	YES	YES	NO	N/A	N/A	NO	N/D	N/D	N/D	N/D	268 DB/M	36.4 KPA
18	1129556	0.3	1.75	34.44	0.07	4.4	NO	N/A	N/A	NO	YES	NO	YES	NO	NO	N/A	N/A	NO	N/D	N/D	N/D	N/D	208 DB/M	22.6 KPA
19	1156876	0.39	0.9	59.47	0.08	2.01	NO	N/A	N/A	NO	NO	NO	YES	NO	NO	N/A	N/A	NO	N/D	N/D	N/D	N/D	223 DB/M	12.8 KPA

					ETIOLOGY						PERSONAL HISTORY		COMORBITIES							EXAMINATION				
S.NO	MRD NO	NAME	AGE	SEX	HEPATITIS B	HEPATITIS C	NON-ALCOHOLIC FATTY LIVER DISEASE	NON ALCOHOLIC STEATO HEPATITIS	INBORN ERRORS OF METABOLISM	AUTOIMMUNE LIVER DISEASE	ALCOHOL	SMOKING	HYPERTENSION	TYPE 2 DIABETES MELLITUS	CORONARY ARTERY DISEASE	CHRONIC OBSTRUCTIVE AIRWAY DISEASE	OBESITY	SEIZURE	PREVIOUS SURGERY	HEIGHT	WEIGHT	BMI	BP	PR
20	1162497	SL	67Y	M	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO	NO	NO	YES	NO	NO	165 CM	75 KGS	27.57KG/M2	130/80MMHG	70/MIN
21	1165531	AS	42Y	M	NO	NO	NO	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO	NO	NO	176 CM	82 KGS	26.6KG/M2	140/80MMHG	100/MIN
22	1166385	GS	50Y	M	NO	NO	NO	NO	NO	NO	YES	NO	NO	YES	NO	NO	NO	NO	NO	180 CM	90 KGS	28KG/M2	110/80MMHG	76/MIN
23	862865	SB	49Y	M	YES	NO	NO	NO	NO	NO	NO	NO	NO	YES	NO	NO	NO	NO	NO	173 CM	85 KGS	28.5KG/M2	130/80MMHG	76/MIN
24	882712	DK	47Y	M	NO	YES	NO	NO	NO	NO	NO	NO	NO	YES	NO	NO	NO	NO	NO	173 CM	76 KGS	25.41KG/M2	130/80MMHG	70/MIN
25	1025285	AV	58Y	M	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO	NO	NO	YES	NO	NO	170 CM	86 KGS	29.8KG/M2	130/80MMHG	72/MIN
26	1112025	SG	60Y	M	NO	NO	NO	YES	NO	NO	NO	NO	NO	YES	NO	NO	YES	NO	NO	172 CM	86.3 KGS	29.2KG/M2	110/80MMHG	76/MIN
27	704522	RS	57Y	M	NO	NO	NO	NO	NO	NO	YES	NO	NO	NO	NO	NO	YES	NO	NO	174 CM	87.8 KGS	29KG/M2	130/80MMHG	96/MIN
28	1161783	BS	52Y	M	NO	NO	NO	NO	NO	NO	YES	NO	YES	YES	NO	NO	NO	NO	NO	173 CM	76 KGS	25.41KG/M2	130/80MMHG	86/MIN
29	1192379	JK	67Y	M	NO	NO	NO	YES	NO	NO	NO	NO	NO	YES	NO	NO	YES	NO	NO	163 CM	77 KGS	29.1KG/M2	110/70MMHG	80/MIN
30	1191733	SS	57Y	M	NO	NO	NO	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO	NO	NO	173 CM	75.7 KGS	25.3KG/M2	130/80MMHG	78/MIN
31	1140560	DS	53Y	M	NO	NO	NO	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO	NO	NO	168 CM	74 KGS	26.2KG/M2	140/80MMHG	86/MIN
32	774335	MS	68Y	M	NO	NO	NO	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO	NO	NO	174 CM	76.2 KGS	25.2KG/M2	130/80MMHG	81/MIN
33	560792	AK	66Y	M	NO	NO	NO	NO	NO	NO	YES	NO	NO	NO	NO	NO	YES	NO	NO	168 CM	76.7 KGS	27.2KG/M2	130/80MMHG	72/MIN
34	870148	JS	53Y	M	NO	YES	NO	NO	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO	NO	170 CM	74.5 KGS	25.8KG/M2	116/80MMHG	72/MIN
35	56553	RS	60Y	F	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	158 CM	61.4 KGS	24.6KG/M2	120/80MMHG	88/MIN

				LIVER DISEASE																					
					DECOMPENSATED																				
S.NO	MRD NO	RR	TEMP	COMPENSATED	ASCITES	JAUNDICE	VARICEAL BLEED	HEPATIC ENCEPHALOPATHY	COAGULATION DEFECT	1. TLC	2. DLC	3. HB	4. PLATELET	5. BILIRUBIN (T)	6. BILIRUBIN (D)	7. SGOT	8. SGPT	9. ALP	10. GGT	11. TOTAL PROTEIN	12. ALBUMIN	13. BLOOD UREA	14. SERUM CREATININE	15. SERUM SODIUM	16. SERIM POTASSIUM	17. SERUM CHLORIDE
20	1162497	16/MIN	98.6F	YES	NO	NO	NO	NO	NO	5500	39.1/42.8/11.6/5.7/0.8	8.8	77000	2.5	1.07	28	15	77	25	6.7	4.29	21	0.99	141	4.06	101
21	1165531	16/MIN	98.6F	YES	NO	NO	NO	NO	NO	8100	57/30.5/10.7/1.1/0.7	9.8	110000	2.14	0.68	86	26	66	535	7.7	2.87	94	3.17	137	4.4	104
22	1166385	16/MIN	98F	YES	NO	NO	NO	NO	NO	9800	41.2/41.4/9.6/7.2/0.6	12.5	102000	1.02	0.56	25	33	77	114	6.4	4	34	0.8	135	4.06	96
23	862865	12/MIN	98.6F	YES	NO	NO	NO	NO	NO	7100	42.3/41.7/10.5/5.4/0.1	15.1	124000	1.43	0.27	59	51	62	36	7.1	3.87	27	0.92	133	3.61	102
24	882712	12/MIN	98.6F	YES	NO	NO	NO	NO	NO	13900	78.8/11.7/7.2/2.2/0.1	14	172000	0.61	0.3	29	48	67	86	6	2.93	53	1.07	134	4.41	101
25	1025285	12/MIN	98.6F	YES	NO	NO	NO	NO	NO	4800	49.2/32.4/10.5/7.8/0.1	11.4	60000	1.6	0.6	46	42	69	80	6.2	3.16	18	0.73	135	4.19	105
26	1112025	16/MIN	98.8F	YES	NO	NO	NO	NO	NO	6900	60.7/24.7/10.9/3.1/0.6	17.5	150000	1.19	0.43	58	70	93	56	7.3	3.79	16	0.74	138	4.26	101
27	704522	16/MIN	98.6F	YES	NO	NO	NO	NO	NO	5200	42.9/39.2/9.3/8.1/0.5	13.7	80000	1	0.28	126	97	54	46	7.4	3.57	20	0.43	141	4.01	108
28	1161783	20/MIN	99F	YES	NO	NO	NO	NO	NO	7300	71.1/17.7/10/1/0.2	9.2	76000	0.88	0.61	98	92	166	744	5.5	2.59	40	0.9	138	5.47	106
29	1192379	16/MIN	99F	YES	NO	NO	NO	NO	NO	7700	40/46.6/9.9/2.7/0.8	10.6	100000	0.68	0.09	201	126	528	128	6.5	3.01	16	0.73	136	5.64	99
30	1191733	16/MIN	98.6F	YES	NO	NO	NO	NO	NO	4200	50.9/35.7/8.3/4.2/0.9	11	60000	0.69	0.13	29	22	98	81	7.1	4.2	20	0.69	140	4.19	109
31	1140560	14/MIN	99.2F	YES	NO	NO	NO	NO	NO	6100	57.4/28.3/10.8/2.9/0.6	10.7	94000	2.3	1.47	92	57	129	17	5.8	2.04	23	0.5	132	4.48	102
32	774335	16/MIN	98.6F	YES	NO	NO	NO	NO	NO	16900	74.4/12.5/10.1/0.5/0.1	11.8	552000	0.69	0.21	95	211	180	97	7.2	3.71	45	0.86	129	5.14	92
33	560792	16/MIN	98.6F	YES	NO	NO	NO	NO	NO	3500	56.3/25.3/10.1/7.7/0.6	10.5	64	2.34	1.36	47	30	104	102	9.2	3.6	30	0.9	131	3.83	97
34	870148	14/MIN	98F	YES	NO	NO	NO	NO	NO	5800	75.3/11.3/10.5/2.6/0.3	7.4	162000	0.71	0.28	54	22	194	71	7.6	2.57	16	0.7	136	3.94	99
35	56553	16/MIN	99F	YES	NO	NO	NO	NO	NO	4000	74.1/12.3/10/3.3/0.3	9.9	80000	0.72	0.33	41	24	150	68	7.4	3.63	30	0.55	141	4.11	107

		LABORATORY																					
							23. ULTRASONOGRAPHY				24. UPPER GI ENDOSCOPY				25. CT SCAN				26. MRI(IF DONE)				27. FIBROSCAN	
											• PHG(+/-)													
S.NO	MRD NO	18. HBsAG(ELISA)	19. ANTI HBC TOTAL	20. ANTI HCV(ELISA)	21. HIV	22. AFP	• SOL(+nt)/(-nt)	• SIZE	• LOBE/SEGMENT	• PVT(+nt)/(-nt)	Mild	Severe	• VARICES(+/-)	• EVL(+/-)	• SOL(+nt)/(-nt)	• SIZE	• LOBE/SEGMENT	• PVT(+nt)/(-nt)	• SOL(+nt)/(-nt)	• SIZE	• LOBE/SEGMENT	• PVT(+nt)/(-nt)	• CONTROLLED ATTENUATION PARAMETER	• LIVER STIFFNESS
20	1162497	0.46	2	0.05	0.19	13.06	NO	N/A	N/A	NO	YES	NO	YES	NO	NO	N/A	N/A	NO	N/D	N/D	N/D	N/D	291 DB/M	74.8 KPA
21	1165531	0.26	1.41	0.06	0.11	6.15	NO	N/A	N/A	NO	NO	NO	NO	NO	NO	N/A	N/A	NO	N/D	N/D	N/D	N/D	280 DB/M	67.5 KPA
22	1166385	0.34	1.76	0.08	0.13	6	NO	N/A	N/A	NO	NO	NO	NO	NO	NO	N/A	N/A	NO	N/D	N/D	N/D	N/D	304 DB/M	19.6 KPA
23	862865	0.08	0.01	0.06	0.13	5.12	NO	N/A	N/A	NO	NO	NO	NO	NO	NO	N/A	N/A	NO	N/D	N/D	N/D	N/D	325 DB/M	14.6 KPA
24	882712	0.47	0.01	4.34	0.2	2.55	NO	N/A	N/A	NO	YES	NO	NO	NO	NO	N/A	N/A	NO	N/D	N/D	N/D	N/D	207 DB/M	18.5 KPA
25	1025285	0.36	1.23	0.07	0.14	54.42	NO	N/A	N/A	NO	NO	YES	YES	NO	YES,BENIGN	9 X 9MM	RIGHT,SEGMENT 7	NO	N/D	N/D	N/D	N/D	298 DB/M	75 KPA
26	1112025	0.39	1.23	0.05	0.24	3.61	NO	N/A	N/A	NO	NO	NO	NO	NO	NO	N/A	N/A	NO	N/D	N/D	N/D	N/D	272 DB/M	21.3 KPA
27	704522	0.17	1.12	0.07	0.08	32.99	NO	N/A	N/A	NO	YES	NO	YES	NO	NO	N/A	N/A	NO	N/D	N/D	N/D	N/D	281 DB/M	30.5 KPA
28	1161783	0.25	1.08	0.05	0.08	6.7	NO	N/A	N/A	NO	YES	NO	NO	NO	NO	N/A	N/A	NO	N/D	N/D	N/D	N/D	202 DB/M	20.6 KPA
29	1192379	0.51	1.55	0.07	0.24	4.2	NO	N/A	N/A	NO	NO	NO	NO	NO	NO	N/A	N/A	NO	N/D	N/D	N/D	N/D	355 DB/M	14.3 KPA
30	1191733	0.41	1.26	0.09	0.16	4.8	NO	N/A	N/A	NO	NO	NO	NO	NO	NO	N/A	N/A	NO	N/D	N/D	N/D	N/D	261 DB/M	13.2 KPA
31	1140560	0.21	1.26	0.06	0.7	2.62	YES	5 X 4.5 CM	RIGHT LOBE,SEGMENT 7 & 8	NO	YES	NO	YES	NO	YES	5.2 X 4.9 X 4.8 CM	RIGHT LOBE, SEGMENT 7 & 8	NO	N/D	N/D	N/D	N/D	286 DB/M	24.1 KPA
32	774335	0.61	1.71	0.09	0.54	5.41	YES	10.3 X 8.7 CM	LEFT LOBE	NO	NO	YES	YES	NO	YES	11.6 X 9 CM	LEFT LOBE, SEGMENT 3	NO	N/D	N/D	N/D	N/D	256 DB/M	72.8 KPA
33	560792	0.37	1.5	0.08	0.2	6.65	NO	N/A	N/A	NO	YES	NO	YES	YES	YES	2.1 X 1.9 CM, 1.7 X 1.2 CM	BOTH LOBES SEGMENT 3 & 6	YES	N/D	N/D	N/D	N/D	211 DB/M	57.6 KPA
34	870148	0.12	1.29	36.44	0.12	17.15	YES		RIGHT LOBE	NO	YES	NO	YES	NO	YES	7.8 X 8.9 X 4.6 CM	RIGHT LOBE,SEGMENT 8	NO	N/D	N/D	N/D	N/D	206 DB/M	69.8 KPA
35	56553	34.16	0.34	0.06	0.12	184.77	YES		RIGHT LOBE	NO	YES	NO	YES	NO	YES	3.1 X 3 CM,1.7 X 1.2 CM	RIGHT LOBE SEGMENT 5 & 7	YES	N/D	N/D	N/D	N/D	269 DB/M	45.6 KPA

					ETIOLOGY						PERSONAL HISTORY		COMORBITIES							EXAMINATION				
S.NO	MRD NO	NAME	AGE	SEX	HEPATITIS B	HEPATITIS C	NON-ALCOHOLIC FATTY LIVER DISEASE	NON ALCOHOLIC STEATO HEPATITIS	INBORN ERRORS OF METABOLISM	AUTOIMMUNE LIVER DISEASE	ALCOHOL	SMOKING	HYPERTENSION	TYPE 2 DIABETES MELLITUS	CORONARY ARTERY DISEASE	CHRONIC OBSTRUCTIVE AIRWAY DISEASE	OBESITY	SEIZURE	PREVIOUS SURGERY	HEIGHT	WEIGHT	BMI	BP	PR
36	882091	MS	61Y	M	YES	YES	NO	NO	NO	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO	174 CM	85.3 KGS	28.2KG/M2	140/80MMHG	88/MIN
37	557062	HK	50Y	F	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	YES	NO	NO	162 CM	74.6 KGS	28.43KG.M2	120/80MMHG	78/MIN
38	884136	SS	65Y	M	NO	NO	NO	NO	NO	NO	YES	NO	NO	NO	NO	NO	YES	NO	NO	168 CM	82.4 KGS	29.2KG/M2	130/80MMHG	76/MIN
39	890580	MN	51Y	M	NO	NO	NO	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO	NO	NO	165 CM	62 KGS	22.79KG/M2	130/80MMHG	76/MIN
40	790116	VK	54Y	M	NO	YES	NO	NO	NO	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO	170 CM	76.2 KGS	26.4KG/M2	146/86MMHG	82/MIN
41	739845	HC	62Y	M	NO	NO	NO	YES	NO	NO	NO	NO	YES	YES	NO	YES	NO	NO	NO	167 CM	81.4 KGS	29.4KG/M2	136/82MMHG	78/MIN
42	898587	SS	55Y	M	NO	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	171 CM	74.8 KGS	25.6KG/M2	124/80MMHG	70/MIN
43	438974	TK	61Y	F	NO	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	160 CM	67.3 KGS	26.3KG/M2	118/80MMHG	76/MIN
44	407857	DJ	67Y	M	NO	NO	NO	NO	NO	NO	YES	NO	YES	NO	NO	NO	NO	NO	NO	170 CM	82.6 KGS	28.6KG/M2	130/80MMHG	86/MIN
45	918707	JS	65Y	M	NO	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	169 CM	70.2 KGS	24.6KG/M2	116/80MMHG	76/MIN
46	910618	GS	61Y	M	NO	YES	NO	NO	NO	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO	170 CM	70.2 KGS	24.3KG/M2	146/86MMHG	92/MIN
47	900196	KS	72Y	M	NO	NO	NO	NO	NO	NO	YES	NO	YES	NO	NO	NO	NO	NO	NO	173 CM	75.7 KGS	25.3KG/M2	140/80MMHG	86/MIN
48	913146	SS	76Y	M	NO	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	167 CM	67.7 KGS	24.3KG/M2	110/70MMHG	70/MIN
49	916098	CP	61Y	M	NO	NO	NO	NO	NO	NO	YES	YES	NO	NO	NO	NO	NO	NO	NO	168 CM	71.1 KGS	25.2KG/M2	118/78MMHG	76/MIN

				LIVER DISEASE																					
					DECOMPENSATED																				
S.NO	MRD NO	RR	TEMP	COMPENSATED	ASCITES	JAUNDICE	VARICEAL BLEED	HEPATIC ENCEPHALOPATHY	COAGULATION DEFECT	1. TLC	2. DLC	3. HB	4. PLATELET	5. BILIRUBIN (T)	6. BILIRUBIN (D)	7. SGOT	8. SGPT	9. ALP	10. GGT	11. TOTAL PROTEIN	12. ALBUMIN	13. BLOOD UREA	14. SERUM CREATININE	15. SERUM SODIUM	16. SERIM POTASSIUM	17. SERUM CHLORIDE
36	882091	16/MIN	98.9F	YES	NO	NO	NO	NO	NO	7700	27/61.4/8/2.7/0.9	12.8	227000	0.55	0.37	98	80	202	108	8.2	2.2	22	0.83	140	4.2	107
37	557062	16/MIN	98.2F	YES	NO	NO	NO	NO	NO	5500	68.6/15.9/11.4/3.7/0.4	10.5	58000	1.14	0.67	46	30	158	82	7.1	3.41	26	0.75	142	4.23	103
38	884136	16/MIN	98.6F	NO	YES	YES	NO	NO	NO	6300	57.2/31.3/9.3/1.4/0.8	9.8	150000	2.8	1.6	72	42	562	274	7.8	3.2	35	1.04	129	4.38	101
39	890580	16/MIN	98.4F	YES	NO	NO	NO	NO	NO	5800	65.8/20.8/10.9/2/0.5	8.4	90000	1.22	0.77	53	31	104	110	5.4	2.75	44	0.8	145	3.45	117
40	790116	20/MIN	98.6F	YES	NO	NO	NO	NO	NO	1900	55.3/26.6/12.6/4.8/0.7	8.4	100000	0.77	0.31	36	32	36	48	7	3.68	21	0.63	139	3.86	106
41	739845	18/MIN	98F	YES	NO	NO	NO	NO	NO	4000	54/30.4/10.3/4.3/0	8.4	130000	1.73	0.82	91	54	97	86	6.2	2.92	64	0.64	128	4.15	99
42	898587	16/MIN	98.6F	YES	NO	NO	NO	NO	NO	5800	39.4/42.5/11.3/6/0.8	9	80000	1.2	0.8	44	26	64	72	6.2	3.2	26	0.8	140	3.8	96
43	438974	16/MIN	98.2F	YES	NO	NO	NO	NO	NO	11100	67.4/10.9/4.4/0.4/0	13	198000	0.76	0.29	114	53	204	56	7.1	2.88	23	1.05	137	4.63	97
44	407857	16/MIN	99.2F	YES	NO	NO	NO	NO	NO	4200	50.3/35.6/10.1/3.3/0.7	8.1	150000	1.55	0.49	50	32	89	81	7.1	3.03	28	0.87	136	4.28	105
45	918707	16/MIN	98F	NO	YES	YES	YES	YES	NO	7400	72.5/16.7/10.4/0/0.4	11.7	167000	2.26	1.21	478	99	229	108	8.1	3.08	41	0.89	132	4.52	96
46	910618	16/MIN	98F	NO	NO	YES	NO	NO	NO	10900	59.1/26.5//10.5/3.2/0.7	13.4	150000	2.37	0.74	82	55	215	115	6.4	2.52	22	0.64	138	3.66	104
47	900196	16/MIN	98F	YES	NO	NO	NO	NO	NO	8000	62.2/21.6/10.1/5.3/0.8	7.7	324000	0.51	0.11	62	29	292	116	6.5	2.81	19	0.69	136	4.63	102
48	913146	14/MIN	98.6F	NO	NO	YES	NO	NO	NO	3600	61.2/18.5/10.3/9.4/0.6	12.4	57000	1.34	0.7	72	75	73	102	8	3.39	23	0.74	136	4.76	81
49	916098	16/MIN	98.8 F	NO	YES	NO	NO	NO	NO	9900	74.3/17.2/5.9/2.3/0.3	10.1	121000	0.55	0.33	71	27	161	67	5.9	2.7	20	0.91	136	4.27	104

S.NO	MRD NO	LABORATORY																					
							23. ULTRASONOGRAPHY				24. UPPER GI ENDOSCOPY				25. CT SCAN				26. MRI(IF DONE)				27. FIBROSCAN	
											• PHG(+/-)													
		18. HBsAG(ELISA)	19. ANTI HBC TOTAL	20. ANTI HCV(ELISA)	21. HIV	22. AFP	• SOL(+nt)/(-nt)	• SIZE	• LOBE/SEGMENT	• PVT(+nt)/(-nt)	Mild	Severe	• VARICES(+/-)	• EVL(+/-)	• SOL(+nt)/(-nt)	• SIZE	• LOBE/SEGMENT	• PVT(+nt)/(-nt)	• SOL(+nt)/(-nt)	• SIZE	• LOBE/SEGMENT	• PVT(+nt)/(-nt)	• CONTROLLED ATTENUATION PARAMETER	• LIVER STIFFNESS
36	882091	3319	0.96	34.81	0.21	44.36	YES	3.7 X 3.3 CM	RIGHT LOBE, SEGMENT 7	NO	YES	NO	YES	NO	YES	3 X 2.2 CM	RIGHT LOBE, SEGMENT 8	NO	YES	4.4 X 3.2 CM	RIGHT LOBE, SEGMENT 8	NO	267 DB/M	68.9 KPA
37	557062	0.82	>1000	0.62	0.6	39.77	NO	N/A	N/A	NO	YES	NO	YES	NO	YES	2.1 X 2.4 CM, 2 X 2.5 CM	RIGHT LOBE,SEGMENT 8	NO	N/D	N/D	N/D	N/D	322 DB/M	46.1 KPA
38	884136	0.28	1.36	0.11	0.22	95.78	YES	3.2 X 2.6 CM, 4.6 X 4.6 CM	RIGHT LOBE,SEGMENT 7 & 5	NO	YES	NO	YES	NO	YES	5 X 4.6 CM	RIGHT LOBE,SEGMENT 6	NO	N/D	N/D	N/D	N/D	298 DB/M	52.4 KPA
39	890580	0.46	1.46	0.13	0.47	221.64	NO	N/A	N/A	NO	YES	NO	YES	NO	YES	1.1 X 0.8 CM, 1.7 X 1.2 CM	BOTH LOBES, SEGMENT 4 & 5	YES	N/D	N/D	N/D	N/D	262 DB/M	41.4 KPA
40	790116	0.45	1.22	62.97	0.31	3.39	NO	N/A	N/A	NO	YES	NO	YES	YES	YES	1.2 X 1.2 CM	RIGHT LOBE, SEGMENT 8	NO	N/D	N/D	N/D	N/D	248 DB/M	63.8 KPA
41	739845	0.45	1.26	0.38	0.31	2063.59	NO	N/A	N/A	NO	YES	NO	YES	YES	YES	6.3 X 4.4 CM	CAUDATE LOBE	NO	N/D	N/D	N/D	N/D	316 DB/M	60.4 KPA
42	898587	0.26	1.8	62.1	0.34	268.4	NO	N/A	N/A	NO	YES	NO	YES	NO	YES	3 X 2 X 2 CM	RIGHT LOBE, SEGMENT 5	NO	N/D	N/D	N/D	N/D	242 DB/M	53.6 KPA
43	438974	0.14	1.21	13.56	0.14	10.08	NO	N/A	N/A	NO	YES	NO	YES	NO	YES	7.5 X 5.7 MM	RIGHT LOBE, SEGMENT 7 & 8	NO	N/D	N/D	N/D	N/D	281 DB/M	56.1 KPA
44	407857	0.46	1.81	0.08	0.21	2.61	YES	4 X 3.5 CM	RIGHT LOBE, SEGMENT 6	NO	NO	YES	YES	NO	YES	3.7 X 3 CM	RIGHT LOBE, SEGMENT 6	NO	N/D	N/D	N/D	N/D	293 DB/M	58.4 KPA
45	918707	0.41	1.25	68.41	0.41	68.48	YES	4.3 X 3.9 CM	RIGHT LOBE	NO	NO	YES	YES	YES	YES	4.6 X 4.3 CM	RIGHT LOBE, SEGMENT 5	NO	N/D	N/D	N/D	N/D	287 DB/M	75 KPA
46	910618	0.31	42.81	2	0.21	230.64	YES	2.9 X 2.7 CM, 2.3 X 1.9 CM	BOTH LOBES, SEGMENT 4 & 5	NO	YES	NO	YES	NO	YES	3.2 X 3.1 CM, 2.8 X 2.3 CM	BOTH LOBES SEGMENT 4 & 5	NO	N/D	N/D	N/D	N/D	256 DB/M	49.6 KPA
47	900196	0.31	1.81	0.4	0.26	16036	YES	INFILTRATIVE HCC	BOTH LOBES	YES	NO	YES	YES	NO	YES	4.1 X 5.8 CM	BOTH LOBES	YES	N/D	N/D	N/D	N/D	276 DB/M	71.6 KPA
48	913146	0.37	1.91	43.31	0.42	62.96	YES	3.2 X 3 CM, 2.8 X 2.7 CM	BOTH LOBES	NO	YES	NO	YES	NO	YES	3.8 X 3.5 CM, 3 X 2.8 CM	BOTH LOBES,SEGMENT 2 & 7	NO	N/D	N/D	N/D	N/D	236 DB/M	53.3 KPA
49	916098	0.56	1.67	0.07	0.29	2479.34	YES	1 CM	RIGHT LOBE	YES	YES	NO	NO	NO	YES	8.4 X 6 CM	RIGHT LOBE, SEGMENT 8	YES	N/D	N/D	N/D	N/D	216 DB/M	32.6 KPA

					ETIOLOGY						PERSONAL HISTORY		COMORBITIES							EXAMINATION				
S.NO	MRD NO	NAME	AGE	SEX	HEPATITIS B	HEPATITIS C	NON-ALCOHOLIC FATTY LIVER DISEASE	NON ALCOHOLIC STEATO HEPATITIS	INBORN ERRORS OF METABOLISM	AUTOIMMUNE LIVER DISEASE	ALCOHOL	SMOKING	HYPERTENSION	TYPE 2 DIABETES MELLITUS	CORONARY ARTERY DISEASE	CHRONIC OBSTRUCTIVE AIRWAY DISEASE	OBESITY	SEIZURE	PREVIOUS SURGERY	HEIGHT	WEIGHT	BMI	BP	PR
50	783015	GS	70Y	M	NO	NO	NO	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO	NO	NO	171 CM	73.6 KGS	25.2 KG/M2	120/80MMHG	76/MIN
51	936307	DS	52Y	M	NO	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	168 CM	73 KGS	25.82KG/M2	130/80MMHG	84/MIN
52	940487	JS	55Y	M	NO	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	170 CM	80 KGS	27.7KG/M2	130/70MMHG	122/MIN
53	1042406	SS	40Y	M	NO	YES	NO	NO	NO	NO	NO	NO	NO	YES	NO	NO	NO	NO	NO	163 CM	73 KGS	27KG/M2	120/80MMHG	78/MIN
54	996728	HS	56Y	M	NO	NO	NO	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO	NO	NO	170 CM	58 KGS	19KG/M2	100/70MMHG	98/MIN
55	1175352	PL	65Y	M	NO	NO	NO	YES	NO	NO	NO	NO	NO	YES	YES	NO	YES	NO	NO	174 CM	90.4 KGS	29.87KG/M2	140/80MMHG	86/MIN
56	858846	BS	56Y	M	NO	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	172 CM	72.7 KGS	24.6 KG/M2	120/80MMHG	84/MIN
57	923912	SS	50Y	M	NO	YES	NO	NO	NO	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO	173 CM	77.2 KGS	25.8KG/M2	130/80MMHG	76/MIN
58	102107	GK	75Y	M	NO	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	160 CM	62 KGS	24.3KG/M2	118/76MMHG	78.MIN
59	331987	BS	62Y	M	NO	YES	NO	NO	NO	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO	170 CM	73 KGS	25.3KG/M2	124/80MMHG	82/MIN
60	929112	DS	61Y	M	NO	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	170 CM	71 KGS	24.6KG/M2	120/80MMHG	82/MIN

				LIVER DISEASE																				
					DECOMPENSATED																			
S.NO	MRD NO	RR	TEMP	COMPENSATED	ASCITES	JAUNDICE	VARICEAL BLEED	HEPATIC ENCEPHALOPATHY	COAGULATION DEFECT	1. TLC	2. DLC	3. HB	4. PLATELET	5. BILIRUBIN (T)	6. BILIRUBIN (D)	7. SGOT	8. SGPT	9. ALP	10. GGT	11. TOTAL PROTEIN	12. ALBUMIN	13. BLOOD UREA	14. SERUM CREATININE	15. SERUM SODIUM	16. SERIM POTASSIUM	17. SERUM CHLORIDE
50	783015	16/MIN	98F	NO	NO	YES	NO	NO	NO	8000	64.1/26.9/6.6/2.1/0.3	13.6	150000	1.89	1.2	77	54	163	67	9.8	3.4	26	0.88	131	5.04	97
51	936307	20/MIN	98.6 F	YES	NO	NO	NO	NO	NO	6200	46.2/36.1/10.6/6.5/0.6	13	150000	2.39	0.5	62	72	152	246	7.2	3.99	25	0.57	145	4.61	103
52	940487	20/MIN	98.6F	YES	NO	NO	NO	NO	NO	3600	55/38/5/2/0	13.5	122000	0.74	0.35	108	231.6	216	309	9.34	4.04	11.4	0.54	132	3.92	105
53	1042406	20/MIN	98.6F	NO	YES	YES	NO	NO	NO	6700	66.6/20.9/10.7/1.4/0.4	12.5	140000	2.3	1.78	172	79	274	178	7.6	2.11	35	0.77	126	4.11	90
54	996728	16/MIN	97F	NO	YES	NO	NO	NO	NO	4700	62.3/28/8.2/1.1/0.4	7.7	140000	0.56	0.12	50	11	138	46	5.3	2.55	41	1.12	138	3.69	111
55	1175352	18/MIN	97.6F	NO	NO	NO	YES	YES	NO	5600	76.3/12.7/8.7/1.8/0.5	8.6	130000	1.22	0.43	79	24	122	86	7.6	3.29	32	1.09	130	3.53	98
56	858846	18/MIN	99.2F	YES	NO	NO	NO	NO	NO	5700	58.7/26.8/9.3/5/0.2	11.7	177000	0.61	0.36	51	61	173	56	7.6	4.12	28	0.93	139	4.2	100
57	923912	18/MIN	98F	NO	NO	YES	NO	NO	NO	4400	49.4/37.4/10.2/2.5/0.5	12.6	70000	2.4	1.8	114	51	57	46	7.4	3.21	13	0.61	133	3.7	96
58	102107	14/MIN	98F	NO	YES	YES	NO	NO	NO	5900	75.9/13.7/8.4/1.5/0.5	9.8	199000	1.21	0.5	154	20	106	61	8.2	3.63	34	0.67	134	4.28	100
59	331987	16/MIN	98F	YES	NO	NO	NO	NO	NO	4200	66.4/23.1/8.9/1.3/0.3	10.1	155000	0.46	0.24	72	55	119	61	7	4.56	13	0.58	134	4.2	100
60	929112	16/MIN	98.1F	YES	NO	NO	NO	NO	NO	3600	59.2/27.5/10.9/2.2/0.2	8.4	100000	0.93	0.56	47	26	131	76	6	3.15	20	0.91	138	3.19	100

		LABORATORY																					
							23. ULTRASONOGRAPHY				24. UPPER GI ENDOSCOPY				25. CT SCAN				26. MRI(IF DONE)				27. FIBROSCAN	
											• PHG(+/-)													
S.NO	MRD NO	18. HBsAG(ELISA)	19. ANTI HBC TOTAL	20. ANTI HCV(ELISA)	21. HIV	22. AFP	• SOL(+nt)/(-nt)	• SIZE	• LOBE/SEGMENT	• PVT(+nt)/(-nt)	Mild	Severe	• VARICES(+/-)	• EVL(+/-)	• SOL(+nt)/(-nt)	• SIZE	• LOBE/SEGMENT	• PVT(+nt)/(-nt)	• SOL(+nt)/(-nt)	• SIZE	• LOBE/SEGMENT	• PVT(+nt)/(-nt)	• CONTROLLED ATTENUATION PARAMETER	• LIVER STIFFNESS
50	783015	0.31	1.72	0.36	0.27	>2479.34	NO	N/A	N/A	YES	YES	NO	YES	NO	YES	1.4 X 1.1 CM	CAUDATE LOBE	YES	YES	1.6 X 1.5 CM, 1.3 X 1 CM	LEFT LOBE, SEGMENT 2 & CAUDATE LOBE	YES	262 DB/M	53.1 KPA
51	936307	0.54	1.16	16.97	0.21	2.92	YES	MULTIPLE	SEGMENT 3	NO	NO	NO	NO	NO	YES	4.5 X 4.5 CM	SEGMENT 3	NO	N/D	N/D	N/D	N/D	210 DB/M	26.3 KPA
52	940487	0.511	0.74	6.15	0.145	31454.69	YES	14 X 14 CM	RIGHT LOBE	YES	NO	YES	YES	NO	YES	74X79X68	5 AND 6	YES	N/D	N/D	N/D	N/D	311 DB/M	23.3 KPA
53	1042406	3200	0.21	0.08	0.31	7859	YES	7 X 7 CM	LEFT LOBE	NO	YES	NO	YES	NO	YES	7.2 X 6.8 CM	LEFT LOBE/SEGMENT 2	NO	N/D	N/D	N/D	N/D	147 DB/M	75 KPA
54	996728	0.45	1.26	0.23	0.1	321	YES	2.8 X 2.5 CM	RIGHT LOBE	YES	YES	NO	NO	NO	YES	3.1 X 2.91 CM	RIGHT	YES	N/D	N/D	N/D	N/D	167 DB/M	18 KPA
55	1175352	0.19	1.12	0.06	0.05	33.05	YES	5.3 X 3.6 CM	RIGHT LOBE	YES	YES	NO	YES	NO	YES	5 X 4 CM, 2.3 X 2.1 CM	RIGHT LOBE, SEGMENT 5 AND 8	YES	N/D	N/D	N/D	N/D	351 DB/M	75 KPA
56	858846	0.31	1.39	149.2	0.24	2.88	YES	3.6 X 3,2 CM	RIHT LOBE, SEGMENT 8	NO	YES	NO	YES	NO	YES	4.1 X 3.5 CM, 1.3 X 1.1 CM	BOTH LOBES, SEGMENT 3 & 8	NO	YES	5.3 X 3.5 CM	RIGHT LOBE, SEGMENT 8	NO	276 DB/M	64.3 KPA
57	923912	0.57	1.46	136.5	0.37	31.15	YES	1.6 X 1.1CM, 1.3 X 0.9 CM	BOTH LOBES, SEGMENT 4 & 8	NO	YES	NO	YES	NO	YES	1.9 X 1.3 CM, 1.5 X 1.1 CM	BOTH LOBES, SEGMENT 4 & 8	NO	N/D	N/D	N/D	N/D	255 DB/M	62.3 KPA
58	102107	0.31	1.8	84.3	0.4	>2479.34	YES	INFILTRATIVE HCC	BOTH LOBES	YES	YES	NO	YES	NO	YES	14.4 X 13.6 X 10.8 CM	RIGHT LOBE, SEGMENT 8	YES	N/D	N/D	N/D	N/D	224 DB/M	75 KPA
59	331987	0.61	1.92	35.36	0.3	3.63	YES	N/M	RIGHT LOBE	YES	YES	NO	YES	NO	YES	ILL DEFINED	RIGHT LOBE	YES	N/D	N/D	N/D	N/D	243 DB/M	68.5 KPA
60	929112	0.64	1.41	42.47	0.26	1210	YES	6.1 X 5.2 CM	RIGHT LOBE,SEGMENT 7	NO	YES	NO	YES	NO	YES	6.7 X 6.1 CM,3X 3.1 CM	RIGHT LOBE AND CAUDATE LOBE, SEGMENT 6 & 7	NO	N/D	N/D	N/D	N/D	246 DB/M	69.6 KPA

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No. BFUHS/2K21p-TH/ 5011 Date 28/1/2021

The Principal,
DMC,Ludhiana

Subject: **Approval of Plan of Thesis.**

This is to inform you that the Faculty of Medical Sciences in its meeting held on 22.01.2021 has approved the plan of thesis of **Dr. Abhinav Garg**, a student of your college for **MD General Medicine** along with the names of Supervisor/Co-Supervisor as under:-

Topic Plan of Thesis
To study the correlation of liver stiffness measurement and hepatocellular carcinoma

Supervisor
Dr. Dinesh Gupta
Prof. & Head,
Dept. of Medicine,
DMCH, Ludhiana.

Co-Supervisor
Dr. Kavita Saggar
Prof. & Head,
Dept. of Radio-diagnosis,
DMCH, Ludhiana.
Dr. Varun Mehta
Prof.,
Dept. of Gastroenterology,
DMCH, Ludhiana.

The student has to submit the three copies of thesis (along with PDF format) , to the Controller of Examinations, BFUHS, Faridkot, at least six months before the commencement of theory examination, if he/she is otherwise eligible to take the examination. He /She must directed to attach a photocopy of this letter with the forwarding letter while submitting thesis to the University along with the letter of approval of University for change of supervisor/Co-Supervisor, change of topic,(if any).

S P Singh
Dr. S P Singh MS(Oph)
Controller of Examinations

Note :

1. ***If any discrepancy found regarding topic of thesis or Supervisor/Co-Supervisor, inform undersigned within one month after issue of this letter.***
2. *The student may submit the thesis as per the schedule already conveyed i.e for May/June examination 30th Nov of the preceding the year of examination and for Nov/Dec examinations 31st May of the year of examination.*

TO STUDY THE CORRELATION OF LIVER STIFFNESS MEASUREMENT AND HEPATOCELLULAR CARCINOMA

THESIS PROPOSAL

FOR APPROVAL OF SUBJECT OF THESIS TO BE SUBMITTED

IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE DEGREE OF

DOCTOR OF MEDICINE

In

MEDICINE

OF THE

BABA FARID UNIVERSITY OF HEALTH SCIENCES

FARIDKOT

NOVEMBER, 2019

DR. ABHINAV GARG

DEPARTMENT OF MEDICINE
DAYANAND MEDICAL COLLEGE AND HOSPITAL
LUDHIANA

ABSTRACT OF PLAN OF THESIS

Title	To Study The Correlation Of Liver Stiffness Measurement And Hepatocellular Carcinoma
For the degree of	M.D. Medicine
Name of the candidate	Dr. Abhinav Garg
Supervisor	Dr. Dinesh Gupta Professor & Head, Department of Medicine, DMC&H, Ludhiana
Co-supervisor	Dr. Kavita Saggar Professor & Head, Department of Radiology DMC&H, Ludhiana Dr. Varun Mehta Professor, Department of Gastroenterology, DMC&H, Ludhiana
Institution	Dayanand Medical College & Hospital, Ludhiana
University	Baba Farid University of Health Sciences, Faridkot

Introduction: Hepatocellular Carcinoma is the the 6th most common cancer worldwide and accounts for ~7% of all cancers. Hepatocellular Carcinoma commonly develops in patients with advanced fibrosis seen in patients of chronic hepatitis B, chronic hepatitis C, non-alcoholic fatty liver disease, non alcoholic steatohepatitis, autoimmune liver disease. Diagnosis of Hepatocellular Carcinoma is usually made with help CT, MRI. Contrast enhanced ultrasound. Current study was planed to evaluate the role of Fibroscan in prediction of Hepatocellular Carcinoma

Aim of Study: To Study The Correlation Of Liver Stiffness Measurement And Hepatocellular Carcinoma.

Materials & methods: The study will include 30 patients with chronic liver disease with Hepatocellular carcinoma and 30 patients with chronic liver disease with no hepatocellular carcinoma. The study will be conducted in patients attending Medicine OPD, Gastroenterology OPD and Patient's admitted in Medicine and Gastroenterology wards at Dayanand Medical College and Hospital, Ludhiana.

Clinical Significance: This study will be helpful in finding that Liver stiffness measurement cut-off values would be useful for screening to identify the high-risk group for Primary HCC development

Keywords: fibroscan, liver stiffness, hepatocellular carcinoma

(Signature)	(Signature)	(Signature)	(Signature)	(Signature)
Candidate	Co-supervisor	Co-supervisor	Supervisor	Principal

CERTIFICATE OF FACILITIES AVAILABLE

This is to certify that the facilities for work on the subject of thesis titled **"TO STUDY THE CORRELATION OF LIVER STIFFNESS MEASUREMENT AND HEPATOCELLULAR CARCINOMA"** exist in the Department of Medicine, Dayanand Medical College and Hospital, Ludhiana and will be provided to the candidate. We will see that the data being included in the thesis are genuine and is collected by the candidate himself/herself under our supervision and guidance.

Supervisor

Dr. Dinesh Gupta
Professor & Head
Department of Medicine
DMCH, Ludhiana

Co-Supervisor

Dr. Kavita Saggar
Professor & Head
Department of Radiology
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Dr. Varun Mehta
Professor
Department of Gastroenterology
DMCH, Ludhiana

Head of the Department

Dr. Dinesh Gupta
Professor & Head
Department of Medicine
DMCH, Ludhiana

Place: _____

Date: _____

APPROVAL PROFORMA
BY RESEARCH & ETHICAL COMMITTEE
DAYANAND MEDICAL COLLEGE & HOSPITAL, LUDHIANA

Name of candidate	Dr. Abhinav Garg
Department	Medicine
Topic of Thesis	To Study The Correlation Of Liver Stiffness Measurement And Hepatocellular Carcinoma
Likely date of appearing in PG examination	2022
Date of enrollment	MAY 14,2019
Name of Head of Department	Dr. Dinesh Gupta
1) Supervisor **2) Co-Supervisor**	1) Dr. Dinesh Gupta 2) Dr. Varun Mehta 3) Dr. Kavita Saggar
Signature of Members of Research Committee with Stamp	**Signature of Members of Ethics Committee with Stamp**
Dr. Jaspal Singh (Professor & Head, Surgery)	Mr. A K Jindal (Member, Ethics Committee)
Dr. Dinesh Gupta (Professor & Head, Medicine)	Dr. Anu Sharma (Professor, Anatomy)
Dr. Sandeep Kaushal (Assistant Dean Academics)	Dr. Deepinder K Chhina (Professor & Head, Microbiology)
Dr. Rajoo Singh Chhina (Dean Academics)	Dr. Neena Sood (Professor & Head, Pathology)
Dr. Gurpreet S Wander (Vice Principal)	Dr. Gurpreet S Wander (Vice Principal)
	Dr. Gagandeep Singh (Secretary, Ethics Committee Professor & Head, Neurology)

Approved: Yes / ~~No~~

Dr. Sandeep Puri
Chairperson
Research Committee

Chairperson
Research Committee

Approved: Yes / ~~No~~

Prof. Arvind Malhotra
Chairman
Ethics Committee

Chairperson
Ethics Committee

BABA FARID UNIVERSITY OF HEALTH SCIENCES, FARIDKOT

PROFORMA FOR REGISTRATION OF SUBJECT FOR DISSERTATION

1	NAME OF THE CANDIDATE AND ADDRESS	Dr. Abhinav Garg Post-graduate Student, Department of Medicine, Dayanand Medical College and Hospital, Ludhiana
2	NAME OF THE INSTITUTE	Dayanand Medical College and Hospital
3	COURSE OF STUDY AND SUBJECT	M.D. MEDICINE
4	DATE OF ADMISSION OF COURSE	14 MAY,2019
5	TITLE OF THE TOPIC	To Study The Correlation Of Liver Stiffness Measurement And Hepatocellular Carcinoma

6. BRIEF RESUME OF THE INTENDED WORK

6.1 NEED FOR THE STUDY

Hepatocellular Carcinoma (HCC) is the 6th most common cancer and accounts for ~7% of all cancers worldwide.[1,2] The development of HCC depends upon various risk factors, including etiology of liver diseases, race, ethnicity, sex, age, and so on. However, the presence of advanced liver fibrosis is the most important and common risk factor in Chronic Liver Disease patients.[1,2]

Chronic liver disease (CLD) is usually related to hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, alcohol intake and hepatic steatosis including non-alcoholic fatty liver disease (NAFLD) and non alcoholic steato hepatitis, autoimmune liver disease, inborn errors of metabolism. [1,2]

Liver fibrosis is common to all chronic liver disease (CLD). With time, this progressive disruption of hepatic architecture can develop into cirrhosis, characterized by "diffuse conversion of normal liver architecture into structurally abnormal nodules" and 80-90% of HCC develop on the background of cirrhosis.[3]

Historically Liver biopsy has been the standard method for assessing liver fibrosis and steatosis in the last few decades. However this method is not widely used in clinical practice because of its invasiveness, risk of complications, patient discomfort, diversity of sampling, and diagnostic variability.[4,5] Pain and hypotension are the predominant complications for which hospitalization is required. Clinically significant intraperitoneal hemorrhage is the rarest but most serious bleeding complications of percutaneous liver biopsy. Inadverent puncture of Gall bladder may lead to choleperitoneum.

Usually Hepaocellular Carcinoma is diagnosed by Ultrasonography, Biochemical markers, Computed tomography, Magnetic resonance imaging and contrast enhanced ultrasonography. These are excelent in diagnosing Hepatocellular Carcinoma however radiation, cost and inter-observer bias are an important drawback.

A recently introduced technique, transient elastography, non invasively measures hepatic elasticity, or stiffness.[4,5] An ultrasound transducer

probe is mounted on the axis of a vibrator. Vibrations of mild amplitude and low frequency (50Hz) are transmitted by the transducer and an elastic shear wave is generated and its propagation velocity in the liver is measured with pulse-echo ultrasound. The stiffer the tissue, faster the shear wave propagates. The propagation velocity of shear waves is directly proportional to the square root of stiffness of liver. Liver fibrosis is considered to be the largest contributor to the liver stiffness thus measured. Transient Elastography measures liver stiffness in a volume that approximates a cylinder 1 cm in diameter and 4 cm in depth, between 25 to 64 mm underneath the skin surface, this volume is at least 100 times bigger than a biopsy sample, and therefore should be more representative of liver parenchyma.[4]

Few studies have validated the relationship between liver stiffness and the presence of HCC. This study is an attempt to add to the pool of research for finding a new non invasive method of investigation for assessing risk assessment of Hepatocellular carcinoma, as TE has the advantage of being painless, rapid(usually less than 5 min) and easy to perform at the bedside or in the outpatient clinic.

6.2 REVIEW OF LITERATURE

Worldwide, liver cancers are the sixth most common cause of the cancer-related death and rank sixth in terms of incident cases.[1,2] World Health organisation has estimated that more than 1 million patients will die from liver cancer in 2030. With a 5-year survival of 18%, liver cancer is the second most lethal tumour, after pancreatic cancer.[1]

Liver cirrhosis and liver fibrosis of any cause increases the risk of HCC, with an annual incidence between 2 and 4%.[1] This risk varies according to cause, geographic area, sex, age, and degree of liver damge. Worldwide HBV is the main cause of HCC. Other causes include HCV, Dietary exposure to aflatoxin B1, NAFLD, NASH, Alcoholic cirrhosis, smoking, inborn errors of Metabolism.[6]

Most of the burden of liver cancer is in developing countries, where almost 85% of the cases occur. Globally, most of the cases of HCC(>80%) occur in sub-Saharan Africa and in Eastern Asia, with typical incidence rates of more than 20 per 100,000 individuals.[6] Southern European countries(such as Spain, Italy and Greece) tend to have mid-incidence levels(10-20 per 100,000 individuals), whereas North America, South America, Northern Europe, and Oceania have a low incidence of HCC(<5.0 per 100,000 individuals).[6] Recent reports indicate that the incidence of HCC is also decreasing in chinese populations in Hong Kong, Shanghai, and Singapore; the incidence in japan is also decreasing.[6] HCC is rarely seen during the first 4 decades of life, except in populations in which HBV infection is hyperendemic.[6] The mean ages of diagnosis with HCC were 55-59 years in China and 63-65 years in Europe and North America. In low-risk populations, the highest incidence of HCC is among individuals aged 75 or older.[6] HCC is predominant among men, with the highest male:female ratios in areas of high incidence that is South Korea(4.1), North Korea(4.1), Vietnam(4.1),Indonesia(4.3) and France(4.8)[6]

In India, information on HCC is inadequate; whatever information comes about the incidence of HCC comes from autopsy data, cancer registries and population based surveillance data.[7] The autopsy data reveals that 0.2-1.9% of autopsy cases had a higher prevalance of

HCC in South-eastern states of India.[7] However, these information have been replaced by cancer registry data in india. In India, the mean incidence of HCC (per 100,000 population) in the four population-based cancer registeries in the nineties was 2.77 for males and 1.28 for females.[8] Paul et al. in there study found that the incidence rate has been estimated to be 1.60 per 100 person-years. The incidence in the newly diagnosed patients of cirrhosis was 3.53 per 100 person-years.[8]

In patients with cirrhosis, HCC can be diagnosed with the use of imaging techniques because of vascular shift that occurs during malignant transformation of hepatocytes, in which benign lesions (eg regenerative and dysplastic nodules) are supplied by branches of the portal system, whereas malignant nodules are supplied from the hepatic artery. This shift translates into a distinctive pattern of hyperenhancement in the arterial phase and washout in venous or delayed phases on contrast-enhanced CT or MRI. This pattern has a sensitivity between 66% and 82% and a specificity higher than 90% for the diagnosis of HCC in patients with cirrhosis and nodules larger than 1 cm in diameter[1]. Contrast enhanced ultrasonography is also used to characterize liver nodules, but its precise diagnostic role is still under investigation.

Transient elastography (TE) is a new non-invasive tool for measuring liver stiffness, which is correlated to the histologic stage of liver fibrosis. Several studies in chronic liver disease (CLD) have determined a good accuracy of TE in predicting significant fibrosis and an optimal accuracy in predicting cirrhosis. Normal liver stiffness ranges between 3.3-7.8 Kpa and using a cut off of 7.1 Kpa, a significant fibrosis and cirrhosis can be excluded with a very high negative predictive value(NPV).[9] In cirrhotic patients, liver stiffness measurements range from 12.5 to 75.5 kPa.[7] J Fouchet et al. in there prospective study showed that transient elastography is an excellent efficient technique for the diagnosis of cirrhosis and its severity. With a cut off value of 17.6 kPa, negative and positive predictive values for the diagnosis of cirrhosis were 92% and 91% repectively. They established the cut off

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values for complications of cirrhosis, with a negative predictive value of more than 90%. These cut off values were 27.5 kPa for oesophageal varices stage 2/3, 37.5 kPa for cirrhosis Child-Pugh B or C, 49.1 kPa for a past history of ascites, 53.7 kPa for HCC, and 62.7 kPa for oesophageal bleeding.[10] In clinical practice such results could be of major relevance for follow up of patients with sever fibrosis or cirrhosis.

Yinghua Zhang et al. determined a significant association between liver stiffness variation and Hepatocellular Carcinoma development in patients with Chronic Hepatitis B with compensated cirrhosis and suggested that liver stiffness by transient elastography is an effective serial assessment for hepatic disease progression.[2]

Takaaki Izumi et al. concluded that in hepatitis C virus patients, the incidence of Hepatocellular Carcinoma development was significantly higher among those with a combination of Liver stiffness measurement >8.0 kPa and CAP <221 dB/m than among those with other values. They also concluded that in non-alcoholic fatty liver disease patients, the incidence of Hepatocellular Carcinoma development was significantly higher among those with a combination of LSM>5.4kPa and CAP<265 dB/m than among others.[11]

Maciej Adler et al. did a 1yr follow up study of 432 cirrhotic patients with LSM >20kPa and concluded that higher LSM values are associated with higher incidence of Hepatocellular Carcinoma risk.[3]

Ryota Mauzaki et al. did a Multivariate analysis and showed that Hepatocellular Carcinoma (HCC) presence was significantly associated with liver stiffness along with other variables age, male, and alpha-fetoprotein concentration. AUROC was 0.805, 0.741, 0.714, 0.673, 0.670 and 0.654 for liver stiffness, alpha-fetoprotein, albumin, prothrombin activity, AST-platelet ratio index, and platelet count, respectively. They concluded that liver stiffness measured by transient elastography is useful in demarcating chronic hepatitis C patients at a high risk for HCC, who require frequent check-up by imaging examinations.[12]

Pierre Nahon et al. did a case control study and found out that patients with Hepatocellular Carcinoma had higher Liver stiffness Measurement

than patients without Hepatocellular Carcinoma[35.3 kPa (22.8-52.6) vs. 19.0 kPa (12.4-29.2), P<0.0001]. They concluded that in patients with Child-Pugh A cirrhosis, a wide range of Liver stiffness measurement is observed according to the cause underlying liver disease and the presence of Hepatocellular Carcinoma is associated with higher values in these patients.[13]

Yuan-hung Kuo et al. demonstrated that Liver stiffness measurement was an independent factor in the prediction of Hepatocellular Carcinoma presence. And the risk of Hepatocellular Carcinoma increased with advancement of cirrhosis. With liver stifffness >24 kPa, the likelihood ratio of Hepatocellular Carcinoma presence was 5.9 for chronic hepatitis patients. The sensitivity and specificity in the prediction of HCC presence was 41.5 and 92.7%, respectively.[14]

Ashraf O. Abdelaziz et al. concluded that progression of Chronic hepatitis C is associated with a decrease in steatosis, particularly toward advanced fibrosis and Hepatocellular Carcinoma. Steatosis reduction less than 237 dB/m is likely to be associated with Hepatocellular Carcinoma.[15]

Takaaki Sugihara et al. did a cross sectional study in residents aged > 40 years in japan and concluded that the combination of controlled attenuation parameter and liver stiffness measurement can be useful in detecting high-risk liver diseases of Hepatocellular Carcinoma out of general population.[16]

Yeon Seok Seo et al. did a cohort study on 381 patients and did a follow up period of 48.1 months. In patients with HCC development, age, proportion of diabetes mellitus, histological fibrosis stage and liver stiffness value were significantly higher than those in patients without. The cumulative incidence rates of HCC increased significantly in association with elevated Liver stiffness value in 3 stratified groups(LSvalue ,8, 8-13 and, > 13 kPa; log-rank test, P,0.001), and with higher histological fibrosis stage in 3 stratified groups(F0-2, F3 and F4; log-rank test, P,0.001). On multivariate analysis, along with age, liver stiffness value was an independent predictor of Hepatocellular Carcinoma development.[17]

Mi Na Kim et al. investigated that transient elastography(TE) can identify patients with subclinical cirrhosis(SCC) who are at increased risk of developing Hepatocellular Carcinoma among chronic hepatitis B(CHB) patients without clinical evidence of cirrhosis. They did a prospective study on 2,876 study on chronic hepatitis B patients without clinical cirrhosis. Subclinical cirrhosis was defined as a non-clinical cirrhosis, but with a liver stiffness(LS) value >13 kPa. On multivariate analysis, Subclinical cirrhosis was independently associated with a risk of developing Hepatocellular Carcinoma, regardless of antiviral therapy. Thus they concluded that Transient elastography can identify patients with subclinical cirrhosis who are at increased risk of developing Hepatocellular carcinoma, even when cirrhosis is not clinicall apparent.[18]

Kyu sik Jung et al. did a prospective study on 1,130 patients with non-biopsy-proven chronic hepatitis B for the role of FibroScan in assessing the degree of liver fibrosis and the risk of development hepatocellular carcinoma. After Liver stiffness measurement was performed, patients attended regular follow up as a part of surveillance program for the detection of Hepatocellular Carcinoma. They concluded that Liver stiffness Measurement could be a useful predictor for Hepatocellular Carcinoma development in patients with Chronic Hepatitis B.[19]

Mi Young Jeon found a significant association between subcirrhotic range of liver stiffness value and lower risk of HCC development was identified in patients with clinically evident CHB-related cirrhosis.[20]

This study was planned to study the role of Fibroscan as a new modality for predicting the risk of development of HCC in patients at risk.

6.3 AIMS AND OBJECTIVES OF THE STUDY

To study the correlation of liver stiffness measurement and development of Hepatocellular Carcinoma.

7. MATERIALS AND METHODS

7.1 Source of Data

Outdoor patient Department (OPD) and wards of General Medicine and Gastroenterology at Dayanand Medical College and Hospital, Ludhiana.

7.2 METHOD OF COLLECTION OF DATA

Cases and control will be selected on the basis criteria set in Inclusion and Exclusion criteria for the study and Fibroscan will be performed in selected patients.

INCLUSION CRITERIA

GROUP A

1. Cirrhosis of any etiology(Compensated and Decompensated)
2. Diagnosis of HCC on either non invasive criteria for a focal lesion defined by the EASL guidline or histological evidence
3. Age more than 18 Yrs

GROUP B inclusion criteria:

- Cirrhosis of any etiology
- Compensated cirrhosis
- No evidence of HCC at the time of inclusion, as assessed by negative ultrasonographic screening or tripahsic CT and MRI(wherever indiacated).

EXCLUSION CRITERIA

1. BMI >30 kg/m2
2. ALT > 10 times of upper limit of normal
3. Patient's with associated heart failure
4. Local skin disease at site where Fibroscan probe will be kept
5. Pregnant women and patients with active implantable medical devices

NO OF PATIENTS

The study will conducted on 30 patients in Group A and B each.

STUDY DESIGN

The study will constitue 2 groups-

Group A: Patients with cirrhosis and Hepatocellular Carcinoma

Group B: Patients with cirrhosis and no Hepatocellular Carcinoma

STATISTICAL ANALYSIS

Data will be described in terms of range; mean ±standard deviation (± SD), frequencies (number of cases) and relative frequencies (percentages) as appropriate. Comparison of quantitative variables between the study groups will be done using Student t-test and Mann Whitney U test for independent samples for parametric and non-parametric data respectively. For comparing categorical data, Chi square ($\chi 2$) test will be performed and exact test will be used when the expected frequency is less than 5. Receiver operator characteristics (ROC) curve will be done, and criterion value will be estimated depending on the specificity and sensitivity. Area under curve (AUC) will be measured. A probability value (p value) less than 0.05 will be considered statistically significant. All statistical calculations will be done using SPSS (Statistical Package for the Social Science) SPSS 21 version statistical program for Microsoft Windows

7.3 DOES THE STUDY REQUIRE ANY INVESTIGATIONS OR INTERVENTIONS TO BE CONDUCTED ON PATIENTS OR OTHER HUMANS OR ANIMALS? IF SO, PLEASE DESCRIBE BRIEFLY.

Yes this study requires FIBROSCAN to be performed on patients with cirrhosis

7.4 HAS ETHICAL CLEARANCE BEEN OBTAINED FROM YOUR INSTITUTION IN CASE OF 7.3?

Attached herewith

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PROFORMA

S.NO.

NAME- AGE-

SEX- MRD NO-

ADDRESS-

CONTACT NUMBER-

ETIOLOGY-

- HEPATITIS B
- HEPATITIS C
- NON-ALCOHOLIC FATTY LIVER DISEASE
- NON ALCOHOLIC STEATO HEPATITIS
- INBORN ERRORS OF METABOLISM
- AUTOIMMUNE LIVER DISEASE

PERSONAL HISTORY-

- ALCOHOL-
- SMOKING-

COMORBITIES-

- HYPERTENSION
- TYPE 2 DIABETES MELLITUS
- CORONARY ARTERY DISEASE
- CHRONIC OBSTRUCTIVE AIRWAY DISEASE
- OBESITY
- SEIZURE
- PREVIOUS SURGERY

EXAMINATION- HEIGHT

WEIGHT

BMI

BP

PR

RR

TEMP

Signautre of Candidate **Signature of Supervisor**

LIVER DISEASE-

- COMPENSATED-
- DECOMPENSATED-
  - ASCITES-
  - JAUNDICE
  - VARICEAL BLEED
  - HEPATIC ENCEPHALOPATHY
  - COAGULATION DEFECT

LABORATORY-

1. TLC
2. DLC
3. HB
4. PLATELET
5. BILIRUBIN(T)
6. BILIRUBIN(D)
7. SGOT
8. SGPT
9. ALP
10. GGT
11. TOTAL PROTEIN
12. ALBUMIN
13. BLOOD UREA
14. SERUM CREATININE
15. SERUM SODIUM
16. SERIM POTASSIUM
17. SERUM CHLORIDE
18. HBsAG(ELISA)
19. ANTI HBC TOTAL
20. ANTI HCV(ELISA)
21. HIV
22. AFP
23. ULTRASONOGRAPHY
    - SOL(+nt)/(-nt)
    - SIZE
    - LOBE/SEGMENT
    - PVT(+nt)/(-nt)
24. UPPER GI ENDOSCOPY
    - PHG(+/-):- Mild
      - Severe
    - VARICES(+/-)
    - EVL(+/-)
25. CT SCAN
    - SOL(+nt)/(-nt)
    - SIZE

Signautre of Candidate **Signature of Supervisor**

- LOBE/SEGMENT
- PVT(+nt)/(-nt)

26. MRI(IF DONE)
    - SOL(+nt)/(-nt)
    - SIZE
    - LOBE/SEGMENT
    - PVT(+nt)/(-nt)

27. FIBROSCAN
    - CONTROLLED ATTENUATION PARAMETER
    - LIVER STIFFNESS

Signautre of Candidate

Signature of Supervisor

मरीज अनुमति फार्म

तिथि _____

मैं _____ पत्नी/पुत्र/पुत्री _____

निवासी _____

इस शोधकार्य **"TO STUDY THE CORRELATION OF LIVER STIFFNESS MEASUREMENT AND HEPATOCELLULAR CARCINOMA"** में भाग लेने के लिए सहमत हूँ। मैं इस शोधकार्य में भाग लेने के लिए अपनी स्वेच्छा से तैयार हूँ। मैं पुष्टि करता/करती हूँ की यह स्वीकृति देने के लिए मुझे कोई आर्थिक प्रलोभन नहीं दिया गया और न ही दबाव डाला गया है। मुझे इस शोधकार्य का उद्देश्य स्पष्ट कर दिया गया है और मुझे यह विश्वास है की यह विज्ञान और मानवता के लाभ के लिए है। मुझे इस शोधकार्य में होने वाले जोखिम के बारे में समझा दिया गया है और मेरी समझ में यह जोखिम बहुत मामुली है।

मैं इस शोधकार्य में भाग लेने के सम्बन्ध में किसी भी समय अपनी अस्वीकृति व्यक्त कर सकता/सकती हूँ और मेरे अस्वीकृति व्यक्त करने का मेरे इलाज पर कोई प्रभाव नहीं पड़ेगा।

_____ _____

गवाह के हस्ताक्षर रोगी के हस्ताक्षर/अंगूठे का निशान

नाम: नाम:

_____

अन्वेषक के हस्ताक्षर

_____

विद्यार्थी के हस्ताक्षर

ਮਰੀਜ਼ ਰਜ਼ਾਮੰਦੀ ਫਾਰਮ

ਮਿਤੀ_____

ਮੈ_____ਪਤਨੀ/ਪੁੱਤਰ/ਪੁੱਤਰੀ_____

ਵਾਸੀ _____

"TO STUDY THE CORRELATION OF LIVER STIFFNESS MEASUREMENT AND HEPATOCELLULAR CARCINOMA" ਤੇ ਚਲ ਰਹੀ ਖੋਜ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਰਜ਼ਾਮੰਦ ਹਾਂ। ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਮੈ ਆਪਣੀ ਮਰਜ਼ੀ ਨਾਲ ਤਿਆਰ ਹਾਂ। ਮੈ ਇਹ ਦਸਣਾ ਚਾਹੁੰਦਾ ਹਾਂ/ ਚਾਹੁੰਦੀ ਹਾਂ ਕੇ ਇਹ ਰਜ਼ਾਮੰਦੀ ਦੇਣ ਵਾਸਤੇ ਮੈਨੂ ਕਿਸੇ ਵੀ ਤਰਾਂ ਦਾ ਲੋਭ-ਲਾਲਚ ਨਹੀ ਦਿੱਤਾ ਗਿਆ ਅਤੇ ਨਾ ਹੀ ਕੋਈ ਦਬਾ ਪਾਇਆ ਗਿਆ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਦਾ ਮਨੋਰਥ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਭਰੋਸਾ ਦਵਾਇਆ ਗਿਆ ਹੈ ਕੇ ਇਹ ਖੋਜ ਵਿਗਿਆਨ ਅਤੇ ਮਾਨਵਤਾ ਦੀ ਭਲਾਈ ਲਈ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਵਿਚ ਹੋਣ ਵਾਲੇ ਖਤਰੇ ਬਾਰੇ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਯਕੀਨ ਹੈ ਕੇ ਇਹ ਖਤਰਾ ਬਹੁਤ ਮਾਮੂਲੀ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਦਾ ਢੰਗ – ਤਰੀਕਾ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ।

ਮੈ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਬਾਰੇ ਆਪਣੀ ਰਜ਼ਾਮੰਦੀ ਕਿਸੇ ਵੀ ਸਮੇ ਵਾਪਸ ਲੈ ਸਕਦਾ ਹਾਂ/ ਸਕਦੀ ਹਾਂ ਅਤੇ ਮੇਰੀ ਰਜ਼ਾਮੰਦੀ ਵਾਪਸ ਲੈਣ ਦਾ ਮੇਰੇ ਇਲਾਜ ਤੇ ਕੋਈ ਅਸਰ ਨਹੀ ਹੋਵੇਗਾ।

_____ ਗਵਾਹ ਦੇ ਹਸਤਾਖਰ

_____ ਮਰੀਜ਼ ਦੇ ਹਸਤਾਖਰ

ਮਿਤੀ_____

ਮਿਤੀ_____

ਪਤਾ _____

ਪਤਾ _____

_____ ਨਿਰੀਖਕ ਦੇ ਹਸਤਾਖਰ

_____ ਸਿਖਿਆਰਥੀ ਦੇ ਹਸਤਾਖਰ

INFORMED PATIENT CONSENT

Date: _____

I.....D/o, W/o, S/o..... .....am willing to participate in the study **"TO STUDY THE CORRELATION OF LIVER STIFFNESS MEASUREMENT AND HEPATOCELLULAR CARCINOMA"** The procedure with its complications has been explained to me in local vernacular language. I have fully understood that no special tests and extra expenditure in any form, merely for the purpose of thesis is being carried out. I am free to opt out the study any time without assigning any reason.

....

Signature of the Witness Signature of the patient

Name:

Signature of Candidate **Signature of Supervisor**